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MANUAL OF PATHOLOGY

COPLIN

MANUAL

OF

PATHOLOGY

INCLUDING BACTERIOLOGY, THE TECHNIC OF POSTMORTEMS, AND METHODS OF PATHOLOGIC RESEARCH

BY

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WITH FOUR HUNDRED AND NINETY-FIVE ILLUSTRATIONS AND TWENTY-THREE PLATES, TEN OF WHICH ARE IN COLORS

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TO

W. W. KEEN, M.D.

EMERITUS PROFESSOR OF THE PRINCIPLES OF SURGERY AND CLINICAL SURGERY

IN THE JEFFERSON MEDICAL COLLEGE,

AS A TOKEN OF RESPECT AND GRATITUDE THIS

VOLUME IS DEDICATED

BY

THE AUTHOR.

PREFACE TO FOURTH EDITION.

In presenting to the profession and students of medicine the fourth edition of this work I wish gratefully to acknowledge the cordial reception accorded the third edition. Although much larger than any preceding revision, and twice reprinted, the book practically has been out of print for over one year. During that time I have occupied my spare moments in revising, rewriting, and rearranging the subject-matter. A number of the old illustrations have been replaced by new, and many original drawings have been added.

My conviction that properly prepared figures are of the utmost importance in elucidating the subject under consideration remains unchanged; in accord with this view the number of illustrations has been increased from three hundred and thirty, to four hundred and ninety-five; practically all those added are original. The colored plates, which first appeared in the last edition, have been continued and the number increased by the addition of others illustrating the parasitology of malaria, and the blood-changes of leukemia. For both sets of additional plates—five in all—I am indebted to Dr. John C. Da Costa, Jr., who kindly placed at my disposal the superb illustrations from his book on "Clinical Hematology."

The chapter on postmortem examinations has been revised and enlarged, and new methods have been introduced in the chapters on technic. Bacteriologic technic has been transferred to the Appendix, in which are also included brief practical summaries of the methods of microscopic examination of the urine, and also the sputum. The technic of blood examination is fully but briefly reviewed in the chapter on blood, with which it properly belongs. Special technic has been distributed throughout the book; whenever it was necessary to adopt any specific means for demonstrating a reaction or for satisfactorily staining morbid products, the method has been given with the consideration of the materials to be treated. The chapters on immunity and on the pathology of infections have been entirely rewritten and more fully illustrated. The relation of poisons to disease production is discussed with some detail, and the recent theories of intoxication, and cytolytic processes, bearing on problems in general pathology, have been deemed important and worthy of incorporation. A chapter on malformations

including teratogenesis, has been added. The new matter has increased the text by about one-third, but, by enlarging the size and diminishing the margins of the page, and by other expedients well known to the experienced publisher, it has been possible to secure a less bulky and, I believe, a more presentable volume.

Extended experience has led to the belief that many readers desire more information than the scope of this work permits, and that often an inquirer after the truth wishes to study the literature of some subject, too briefly considered in a text-book or manual. To meet this demand I have inserted, in the present edition, numerous references to original articles, usually selecting those papers to which a fuller bibliography is appended. In no case are the references complete, or even exhaustive, but practically all are to recent communications; few only are to publications antedating the year 1900. Wherever possible I have given references to an article in German, another in French, and still another in English; occasionally acceptable articles in other languages are mentioned. As the literature available for most practitioners and students is largely in English, many of the references are to publications in that language.

The chapter on diseases of the nervous system, originally written by Prof. H. F. Harris, has been fully revised and contains considerable new matter. Dr. Alfred Gordon, Instructor in Neuropathology in the Jefferson Medical College, has kindly loaned me a number of exceptionally good illustrations and made valuable suggestions in completing the revision of this part of the work.

The labor incident to revision has been lessened—indeed revision at this time was rendered possible—by the cooperation and cordial assistance of a corps of fellow-workers who generously gave time and effort, particularly by relieving me of the onerous duties incident to supervision of a busy Clinical Laboratory. To these gentlemen—Dr. Aller G. Ellis and Dr. John Funke—I wish to make a most grateful acknowledgment of my indebtedness. Dr. Ellis revised the chapter on the blood. I am also under obligation to Dr. Randle C. Rosenberger for aid in the compilation of stain reactions and biologic peculiarities of the bacteria. Dr. Frederick J. Kalteyer has aided by kindly loaning specimens for illustrations. The table on the blood occupying pages 428 and 429 is largely the product of his energy. Mr. Clark Evans has prepared the index.

Many of the new drawings are by Miss S. L. Clark, whose skill is attested by the results attained. The reproduction of the new illustrations, both colored and uncolored, has been trusted entirely to the publishers, to whom the author is under many obligations for the careful execution of this most difficult task, and for other courtesies.

In conclusion the author wishes to state that the object of the book has not been changed, and that the present edition, although greatly enlarged, remains exactly what the author intended the previous editions to be: namely, "not a treatise or book of reference, but, as its title indicates, a manual that the author hopes may be useful in the laboratory and postmortem room and in clinical diagnosis by the aid of the microscope."

W. M. L. C.

NOTE TO PRESENT REPRINT OF FOURTH EDITION.

The author shares with the publishers the conviction that a "new" edition should mean rewritten chapters, new illustrations, additions, new type and practically a new book. In each of the three revisions that have been issued such an ideal has been constantly in mind. The first issue of the fourth edition was exhausted at a time when pressure of other duties precluded revision and consequently the book was reprinted without alterations. It contained errors which I could not think of perpetuating and consequently when the publishers informed me that another passage through press was necessary I availed myself of the opportunity to make many corrections and additions. Numerous references have been supplanted by more recent ones and a few have been added. Errors of importance, so far as they came to my notice, have been corrected; several illustrations have been replaced by others believed to be more helpful, and thirteen plates embracing twenty-two new figures have been added. Extended study of the typhoid, colon and paratyphoid groups required reconstruction and extensive revision of the tabulated matter referring to the organisms mentioned; for this improvement I am indebted to Prof. Rosenberger. Changes were needed in the paragraphs dealing with the subjects of syphilis, leprosy, anterior poliomyelitis, and several less important diseases. In all, some three hundred pages have been touched up here a little, there extensively. It is hoped that the alterations will render the volume more acceptable to teachers, the profession and medical students, to all of whom the author is profoundly grateful for their generous acceptance of this unpretentious volume.

W. M. L. C.

PREFACE TO SECOND EDITION.

During the winter of 1894 and 1895, Messrs. P. Blakiston, Son & Co. published, in serial form, abstracts of the writer's lectures, entitled "Lectures on Pathology." At the close of the college session the fasciculi were bound, and the resulting volume placed on the market. Very much to the surprise of the publishers, as well as of the writer, the edition lasted less than nine months. It was exhausted at a time when the teaching of the college year precluded the revision which the matter so much needed. During the past six months the entire book has been revised, the larger part having been entirely rewritten. The first edition contained 250 pages and 51 illustrations; the present volume, in the face of every effort to condense without sacrificing accuracy, has reached 638 pages and contains 268 illustrations. The most difficult problem has been to keep the volume from assuming undesired dimensions, and, now that the work is completed, the writer wishes to say, parenthetically, that a volume of twice the size could have been produced with probably less labor. Being practically a new book, there are, no doubt, typographic and grammatic errors. The writer acknowledges in advance his appreciation of any communication calling his attention to such lapses.

In the publication of the original fasciculi the writer was favored by the aid of Professor Kyle and Dr. Bevan. Professor Kyle wrote the fasciculus on "Tumors," and Dr. Bevan the article on "Bacteriology." In the revision of the work both articles have been somewhat enlarged, but the thoroughness of the original has not demanded any extensive revision. There have been made some additions and a rearrangement of subjects, in order to secure greater conformity with the remainder of the book. In the original, acknowledgment of the assistance was given with the fasciculi; it is now incorporated here.

Practically, all the added illustrations appear for the first time in a work on pathology in the English language. The source is credited with each cut. Of the original illustrations it is not the author's province to speak. They have been prepared in the writer's laboratory from specimens and slides of which the clinical and pathologic histology were fully known. In this connection the writer wishes to acknowledge the invaluable assistance of Professor H. F. Harris, who personally super-

intended the execution of most of the original drawings. Miss E. G. Harding, artist, has, with great patience, made the original drawings, often redrawing an illustration a number of times before submitting it for approval.

* * * * * * * * * * * *

In conclusion, the writer wishes to submit the volume, not as a treatise or book of reference, but, as its title indicates, as a manual that he hopes may be useful in the laboratory, postmortem room, and in clinical diagnosis by the aid of the microscope. To attain as fully as possible the last-named aim, the chapters on the microscopic examination of tissues, blood, and urine have been most fully illustrated.

Thanking the profession for its kindly reception of the previous edition, this volume is respectfully submitted for consideration.

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POSTMORTEM TECHNIC.

PART I.—TECHNIC.

CHAPTER I.

POSTMORTEM EXAMINATIONS.[1]

I. INSTRUMENTS NEEDED.

A postmortem may be made with a very few instruments; those supplied in an ordinary dissecting case may suffice for the examination unless the central nervous system is to be removed, in which case a saw will be found necessary. Scarcity of instruments is rarely a justifiable excuse for failure to avail one's self of an opportunity to hold a postmortem. A most thorough examination may be made with a knife such as is ordinarily used by butchers, a saw, and a carpenter's hammer and chisel.

The instruments and appliances given in the following list may be procured by those who contemplate making postmortems, the extent of their purchase being largely a matter of taste and money available. The instruments marked by an asterisk are considered indispensable, the others being conveniences to facilitate or lessen the labor:

* One Virchow postmortem knife.

* Two strong scalpels.

* Two small scalpels; one probe-pointed.

One costotome, or, when this can not be obtained, a cartilage knife or a saw may be substituted.

* At least two dissecting forceps: one with corrugated blades and one with rat-toothed blades. A number of such instruments will be found useful.

* One pair of scissors: one blade sharp and one probe-pointed.

One enterotome, or, when this is not available, a small cork or piece of wood may be pushed over the tip of the sharper pointed blade of the ordinary scissors.

Two long probes: one should have an eye and one should be quite slender; the latter is convenient for tracing ducts. An instrument to be commended is a combined grooved director and probe. For the examination of sinuses and whenever it can be employed, there is no instrument that can be used to better advantage than the trained finger.

* One saw with a well-bellied cutting-edge.

* One grooved director.

[1] The student wishing to add to the following epitome of postmortem technic should consult "La Pratique des Autopsies," by Letulle, "Manuel théorique et pratique des autopsies," by Zilgien, "Pathologisch-anatomische Diagnostick," by Orth, "Sections-Technik," by Nauwerck, "Postmortem Pathology," by Cattell, "Pathological Technique," by Mallory and Wright, and "Die pathologisch-histologischen Untersuchungsmethoden," by Schmorl.

* Two large postmortem needles.

* Two spools of flaxed thread: one white, one black.

* One mallet; the rawhide mallet has the advantage of making but little noise when used on the chisel. The steel hammer ordinarily supplied with postmortem cases has a blunt hook on the handle, which is useful for removing the calvaria, and occasionally for other purposes. The objectionable noise made by pounding on a metallic chisel may be overcome, at least partly, by covering the chisel with a folded towel.

One chisel. Of the various forms of chisels recommended, the lower one in figure 22 will be found most useful. Some of the forms of hatchet-chisel, however, will be occasionally used.

A brass or German-silver ruler, graduated in inches and in centimeters, will be found useful. Such a ruler should be at least twenty centimeters in length, and the graduation throughout should be in tenths; a finer graduation on instruments of this kind can rarely be read at the postmortem table. As a result of attempts to reduce the number of instruments contained in the postmortem case, the writer

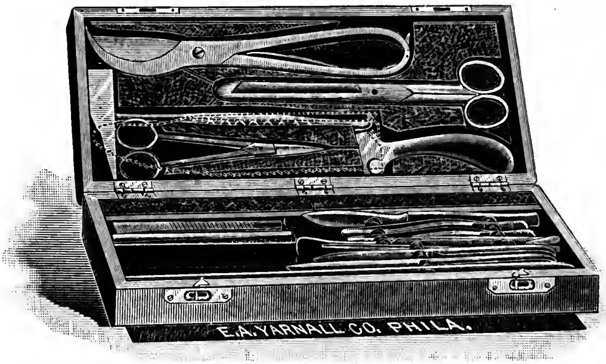

FIG. 1.—COMPLETE POSTMORTEM CASE.
It is convenient to have a leather covering for the case.

has had the long, thin-bladed brain knife, shown in figure 14, graduated along its back. As the instrument is useful for incising organs, the graduation is convenient and always at hand.

A double rachiotome is a very useful instrument, but is not, however, convenient for carrying to private postmortems.

A strong bone forceps will occasionally be needed.

Measures of Capacity.—Small graduates measuring from 0.1 c.c. to 50 c.c. will be found useful. Larger measures should be at hand. Any agateware or tin vessel (the former is preferable) may be standardized by a smaller graduate, and being very much less fragile and less expensive, is therefore to be preferred.

A syringe for sucking up fluid from the bottom of cavities not easily accessible is a convenience.

Postmortem Room.—In well-appointed hospitals, morgues, etc., a room is usually set apart for postmortems. This room should be well lighted and capable of thorough ventilation. The floor should be of impermeable concrete, the walls tiled or built of enameled brick, or, in the

absence of these, covered by lusterless white enamel paint. A capacious postmortem table should be so placed in the room as to be well lighted and accessible on all sides. The size of the table is often a matter of individual preference. The table preferred by the writer is three feet wide, six feet long, substantially constructed, zinc or slate covered, the covering slightly raised at the edges of the table, and the top gently sloping toward a large grate-covered drain in the center. This drain, thoroughly trapped, may be directly connected with the sewage pipes, and may be so attached to the ventilation system as to secure a strong downward draft, thus drawing downward all odors which would otherwise rise and permeate the room. For convenience in measurements a centimeter and inch scale may be ruled upon the edge of the table.

Although never to be used when it can be avoided, an abundance of artificial light should be at command. The best artificial light for the postmortem room is afforded by Welsbach burners with porcelain reflector and shade or Nernst incandescent electric bulbs; thirty-two candle-power incandescent lamps with thoroughly frosted globes are objectionable substitutes for natural light. All forms of artificial light so modify the color of organs as often to afford misleading pictures to the uninitiated.

Water-supply.—Suspended just above the autopsy table and coming down to within an inch or so of the table should be a rubber hose connected with proper metallic fixtures, so arranged as to afford a mixing device, by means of which hot and cold water can be mixed and delivered through the rubber tube at any temperature that may be desired. By permitting the rubber tube to project practically to the table the end can be kept in a pan, thus affording a small reservoir of constantly clean water. The flexible rubber hose affords facilities for washing the table and cleaning the instruments and appliances.

A capacious sink in some part of the room is desirable; into this should drain a slate dripping-slab sixty centimeters wide and two meters long.

Two scales should be at command—one for weighing from a fraction of a gram to ten or twenty grams, the other for heavier masses. Although rarely at hand, a scale for weighing bodies is desirable. Scales for weighing organs and tissues should have large brass pans that can be readily cleaned.

A head block twelve inches long and six inches square, with a notched depression near the center for receiving the neck, will be found useful in supporting the head, and similar blocks may be used for arching the body during the examination of the spine and the removal of the cord.

Heavy boards, fifty by sixty centimeters, will be found serviceable for the support of organs during section.

A vise will be occasionally needed.

Of the various forms of head holders in the market, the writer has never felt that any was better than the hand.

Every well-equipped postmortem room has a book for recording the data obtained at postmortems. This book is usually made up of printed sheets, having a heading arranged according to some definite form which has been adopted by the pathologist. Such headings are useful in making it reasonably certain that no matter who makes the postmortem, the customary routine will be followed. The volume

should not contain a very large number of pages, certainly not over four or five hundred, as a large number would make it too bulky for convenient handling; nor should the sheets be too large. The book to which the writer is accustomed has a page forty centimeters long by twenty-eight centimeters wide, and has printed on each alternate page the form given at the foot of this page. At the time the book is printed it is well to have two or three hundred sheets left unbound, so that at postmortems made outside the institution it will not be necessary to carry the book.

II. PRELIMINARY DATA.

Before beginning the postmortem it is desirable to know and record the name; age; residence, or, in hospital cases, the ward and bed; sex; color; date and hour of death; date and hour of postmortem; methods of preservation if any have been used; the clinical diagnosis; the name and residence of the physician, if any, who last attended the case, and, if possible, his presence should be had at the postmortem.

In medicolegal cases the body should be identified. If the time at which death took place is not known, it may be approximated by the postmortem evidences.

III. THE POSTMORTEM.

In order that the record of a postmortem may be perfect, it is absolutely necessary to follow a definite method in each case. If circum-

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APPROVED FORM OF POSTMORTEM BLANK.

[Name of Institution.]

POSTMORTEM.

Ward________________ Register No.________________

Name, Age, and Sex of Patient________________________Color________________

Physician or Surgeon______________ | Residence ________________________

Resident Physician________________ | Birthplace________________________

Date and Hour of Death____________ | Date and Hour of Postmortem ______

Clinical Diagnosis. ______________________ / ______________________ / ______________________

Pathologic Diagnosis. ______________________ / ______________________ / ______________________

When possible, it is desirable that the following order of examination and recording the postmortem shall be followed:

I. External examination:
Evidence of injury. General nutrition. Ante- or postmortem marks, etc.

II. Internal examination.
1. Abdominal Wall.
2. Peritoneum.
3. Pleuræ.
4. Pericardium.
5. Heart.
6. Lungs.
7. Larynx; Trachea; Bronchi.
8. Thymus; Thyroid.
9. Spleen.
10. Adrenals and Kidneys.
11. Bladder and Internal and External Genitals.
12. Stomach and Duodenum.
13. Liver.
14. Pancreas.
15. Intestines.
16. Esophagus.
17. Vena Cava and Aorta.
18. Head.
19. Spinal Cord.
20. Miscellaneous.

stances demand a variation from this routine method, the *reason for varying should constitute a part of the record.* The following presents nothing original, and is the method adopted by the writer:

(A) The Date and Hour of the Postmortem.

(B) External Examination of the Body.

(*a*) *Is the body dead?* The following observations should be made and recorded as a part of the postmortem notes, as they cover not only the signs of death, but constitute a part of the evidence of diseased conditions: (1) Examine for evidence of respiration and circulation. (2) Look for opacity of the cornea, loss of sensibility in the conjunctiva, pupillary reaction, which may, in doubtful cases, be tested by atropin or eserin; if the eyes are sunken, with wrinkled tunics, the evidence is clear. (3) Pallor of the body may or may not be present, and while valuable as a sign of death, it may be found in the living during swooning, the algid state of ague, collapse, etc. (4) Cooling of the body to the temperature of the surrounding medium (*algor mortis*) occurs in from fifteen to twenty-four hours. The bodies of children and old and lean bodies cool quite rapidly, while bodies of fat, young, and middle-aged individuals retain the heat much longer. The bodies of persons dying from suffocation, electricity, tetanus, and yellow fever very slowly yield their heat. (5) *Cadaveric rigidity*, or *rigor mortis*, occurs at a varying interval after death. It may become manifest but a few minutes after death, or it may be delayed eighteen or twenty hours; usually, it develops simultaneously with the loss of body heat. The duration of rigor mortis is extremely variable, lasting in some instances but a few moments; in other cases, hours, days, or even weeks. (6) *Cadaveric lividity* (the cadaveric blotches called *livores mortis*) and *suggillation* are terms applied to the livid or violet-colored discoloration which is seen usually several hours after death. It becomes apparent in the most dependent portion of the body, and is the result of blood gravitating into the capillaries. (7) *Putrefaction* is an indubitable sign of death. The time at which it becomes manifest varies greatly, and is dependent upon the condition of the body, the surrounding media, and the cause of death. (8) Experimentally, we may infer that the body before us is dead by injecting ammonia water under the skin; in death such a procedure leaves no mark, but in simulated death it occasions a deep red or purple spot. A dead body can not be blistered. Brissemoret and Ambard state that acidity of the tissues is an indubitable sign of death. Icard suggests the subcutaneous injection of 0.5 gm. of fluorescein which, if life be present, rapidly stains the skin, eyes, mouth, urine, and saliva. The iodids may be similarly used in the saliva or urine examined for iodine.

(*b*) *General Considerations.*—The amount of adipose tissue, the muscular development, and the nutrition of the body should be carefully noted, and the record completed or verified as the internal examination proceeds. In case the body has not been identified an elaborate description should be made for the purpose of further identification: the height, weight, measurement of chest, limbs, hands, and feet, color of eyes and hair should be noted, and of the last some should be preserved. A careful survey of the mouth as to dental peculiarities, absence of teeth, filled or irregular teeth, or, better, a dental impression taken in wax or plaster, should be made. If false teeth are present, they

should be removed as possible aids to future identification. Abnormalities, malformations, marks of any kind, should be noted, and, when possible, a photograph of the nude body should be obtained. Such data may, with perfect propriety, constitute a part of any postmortem record; indeed, they are desirable although rarely incorporated in the protocol. Except in the cases mentioned they might have little value in any given postmortem, but in the compilation of important data based of necessity on a large number of cases—*e. g.*, the size and weight of organs as compared with the height and weight of the individual—such records would become invaluable.

(*c*) *Evidence of Violence or Disease.*—*Ecchymoses* should be carefully described as to size, shape, and position. This form of discoloration may be distinguished from *suggillation* in that it does not disappear on pressure, and if an incision be made into it, bloody fluid will escape, or a clot may be discovered in the subcutaneous tissue. All abrasions, eruptions, bed-sores, ulcers, cicatrices, wounds, edema, pigmentations in the skin and mucous membranes must be accurately described, and their positions carefully recorded. Fractures and dislocations must be closely observed, and their character and the parts involved described. The external orifices of the body should be examined, and their condition and contents noted—*e. g.*, mouth and nose for foreign bodies, evidences of corrosive poisoning, etc.; in the female, the breasts, abdomen, and

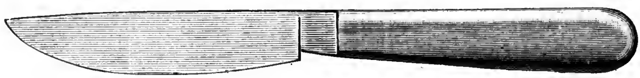

FIG. 2.—MODIFIED VIRCHOW POSTMORTEM KNIFE.
Twenty-four centimeters long, of which 9.5 cm. is cutting-edge.

external genitals should be examined for evidences of disease, violence, or physiologic processes, such as menstruation, recent delivery, or evidences of past gestation, as shown by the mammæ, abdomen (linea albicantes), or external genitals; in the male look for evidence of malformation of the sexual organs or venereal disease, also seminal stains. Examine the anus for fissures, inflammation, fistulæ, morbid growths, cicatrices, etc. Examine the hernial outlets for evidences of rupture.

If the body is that of an infant, examine the fontanels and sutures, and note the various diameters of the skull. Measure the body and examine the umbilical cord. In the male the scrotum should be examined to determine if the testicles have descended; note, also, the presence or absence of vernix caseosa. Carefully examine the epiphyses, and especially that of the lower extremity of the femur.

(C) Internal Examination of the Body.

The large Virchow knife is used for most of the incisions; it is grasped firmly in the hand by the thumb, middle, ring-, and little fingers, while the index-finger rests upon, or at the side of, the blade. Cuts are made with a drawing movement, the shoulder- and elbow-joints acting as centers, the wrist and fingers rigid. Pushing the knife through a tissue or organ, as one would a chisel, is to be avoided, and equally objectionable are sawing and hacking. In ordinary dissection a scalpel is held like a pen, motion being at the joints of the fingers and wrist—a process

entirely too tiresome and slow for postmortem work except when very delicate dissections are to be made.

The body rests firmly upon the back, and the operator, if right-handed, stands to the right of the cadaver. To expose the abdominal and thoracic cavities, an incision should be carried from the lower border of the thyroid cartilage, or from the interclavicular notch, to the symphysis pubis, making a sharp semicircular turn to the left at the umbilicus in order to avoid injury to the remains of fetal organs at that point. The point in the neck at which to begin the incision will be determined by circumstances over which the operator commonly has no control. If he can select the starting-point of his incision, he will ordinarily begin just under the chin, or may even make a Y-shaped cut extending to the angle of the jaw on either side; this permits a most careful examination of the floor of the mouth, pharynx, larynx, and adjacent structures. So extensive a dissection is rarely permissible; in most instances the loosened skin can be retracted upward in such a manner as to permit the

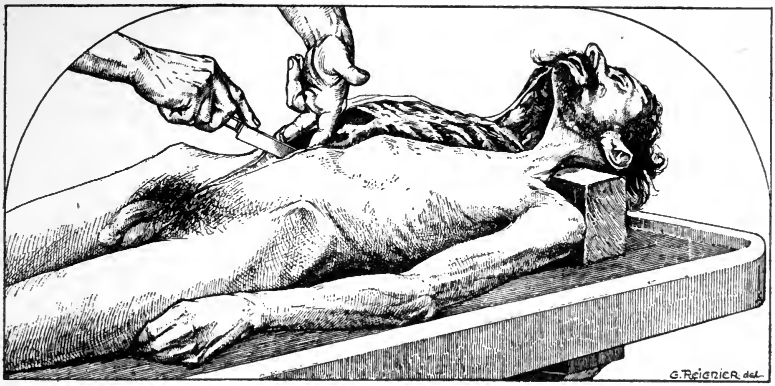

FIG. 3.—MEDIAN INCISION, SHOWING METHOD OF OPENING THE ABDOMINAL CAVITY.—(*Letulle.*) Ordinarily it is not possible to extend the incision to the chin, in which case it does not go beyond the interclavicular notch.

removal of the tongue when the vertical incision does not rise above the level of the thyroid cartilage. Still, as before stated, circumstances, more commonly than any arbitrary rule, will settle this point.

Over the abdomen, the first incision should pass through the skin and subcutaneous tissue; then carefully cut through the abdominal wall immediately below the ensiform cartilage; insert two fingers of the left hand, drawing the abdominal wall upward; continue the incision, the fingers being used as a guide to the knife. A most excellent rule, never to be forgotten by the beginner, is to always keep the point of the knife in view, or, if this is not possible, it should be guarded. If the novice makes it a rule never to cut anything until he has identified it and determined what are its relations, using touch possibly more than sight to establish these facts, he will often be astonished at the dexterity which he quickly acquires and the rapidity with which his senses become trained to recognize the tissues before him. Note the amount and color of the subcutaneous fat in the abdominal wall, its consistency, and

the presence or absence of edema. Examine the muscles for pallor, hyaline spots, degenerative changes (such as occur in typhoid fever), and small white ovoid bodies, encysted trichinæ. Dissect the tissue from the chest-walls as far back as the junction of the costal cartilages with the ribs; then make strong traction on the abdominal walls to break up the rigor mortis. After breaking up the rigor mortis the

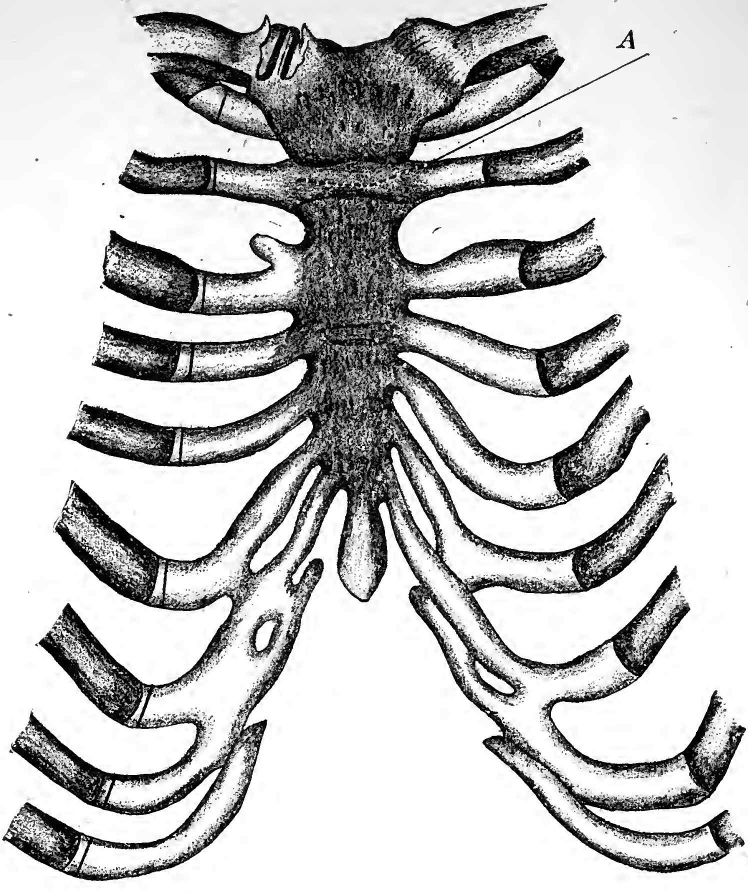

FIG. 4.—THE STERNUM, COSTAL CARTILAGES, AND ARTICULATION OF THE CLAVICLE, AS EXPOSED AFTER TURNING BACK THE SOFT PARTS.—(*Modified from Virchow.*)

On the left is shown the line of incisions made through the cartilages from below upward, if a costotome is used; from above downward, if a knife or saw is employed; and also the incision necessary for disarticulating the clavicle. When it is not desirable to disarticulate the clavicle, the manubrium is separated from the gladiolus at point *A*, the incision being made from behind.

muscles can be further incised, and examined for evidences of bruises, inflammation, and suppuration, and suspicious portions removed for microscopic study.

In the Paris Morgue[1] the incision used begins immediately beneath

[1] Paris letter in the "Boston Medical and Surgical Journal," May 19, 1898, p. 482.

the chin, passes over the larynx and trachea, sweeps across nearly to the left anterior axillary line, which is followed to the crest of the pelvis, is carried along the upper anterior border of the pelvis to the right anterior axillary line, thence to the anterior margin of the right axilla, and finally to the starting-point. In the presence of special conditions such an incision might be advantageous; in most instances it is clearly unnecessary.

Abdominal Cavity.—First note the relative position and color of the liver, stomach, and intestines; and also the relations of the viscera to the costal and ensiform cartilages. The examination of the cavity is not of the organs individually, but of their relation to one another and to the walls; also examine the serous membrane—the peritoneum. A careful search should be made for adhesions and other evidences of inflammation, recent or old, and for thickening and opacity of the serous membrane. The amount and character of any fluid in the cavity must be noted, and, if in excess or otherwise abnormal, the source or cause of the morbid condition must be sought. The color of the liver should be observed before those changes incident to the oxidation of the blood occur. Search carefully for perforations of

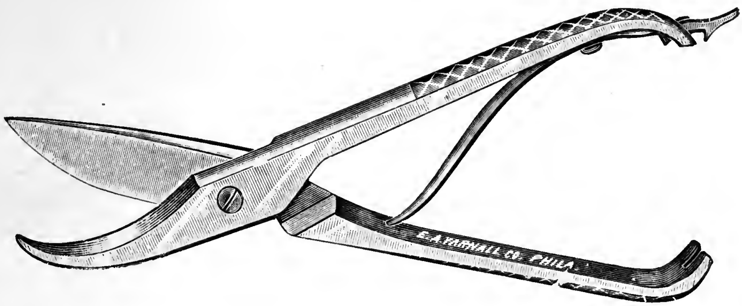

Fig. 5.—Costotome.

the bowel, stomach, bladder, or gall-bladder, whenever the fluid in the cavity is abnormal. Note accurately the position of the diaphragm· ordinarily, on the right side it ascends as high as the fourth rib or interspace; and on the left, to the fifth rib. Remove any fluid present in the cavity before opening the thorax, otherwise fluids in the abdomen flow into the thoracic cavity and thereby complicate the examination.

In infants the umbilicus must be examined carefully; the attached cord or part of the cord and the fetal vessels should be closely inspected and fully described; so far as possible, the vessels should be examined for evidences of infection, thrombosis, and obliteration.

Thoracic Cavity.—In the new-born when it is important to determine if respiration had been established or if air had entered the lung it is well to ligate the trachea as soon as the first incision is made and before opening the abdominal cavity; such precaution prevents air from being drawn into the lungs by traction on the diaphragm or raising the breastplate. With a heavy knife, or costotome (or, in the absence of the latter, when the cartilages are calcareous, a saw may be used), sever the costal cartilages close to the ribs, care being exercised not to injure

the tissues beneath. If the costotome is used, the blade inserted beneath the cartilage should be made to hug that structure closely; if a knife or saw takes the place of the costotome, the incision through the cartilages should begin above, and before one cartilage is completely severed, the blade or shank of the instrument should be made to rest on the next cartilage, thus preventing sudden thrusts which may wound underlying structures. When the last cartilage is reached, it should be gently raised by the unoccupied hand, at the same time depressing the underlying structure, thereby avoiding the danger of wounding the latter.

Divide the attachment of the diaphragm, raise the sternum, and dissect off the attached tissue, taking care to direct the edge of the knife toward the bone in order to avoid injury to the pericardium or other intrathoracic tissues. Cut the ligaments binding the clavicle to the sternum, divide the sternal attachment of the sternocleidomastoid muscle, and pull the breastplate to one side. In a cadaver in which the section of the thorax has been made as just directed, the shoulders having lost the support of the clavicle through their sternal attachment collapse together, making the chest appear very much distorted. To avoid this, in cases where the body is to be viewed, the manubrium and gladiolus may be disjointed by drawing the edge of the knife across the under surface of the articulation of the manubrium and gladiolus (see Fig. 4, p. 25) and raising the lower segment of the sternum.

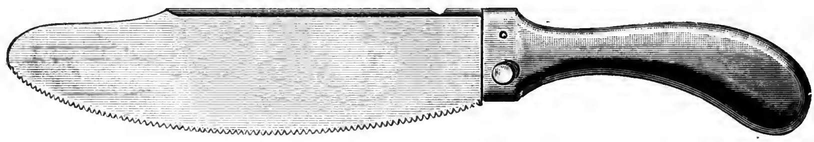

Fig. 6.—Saw.
A large firm handle is wanted, with good pistol grip.

Examine the pleuræ for evidences of inflammation, either remote or recent; note presence or absence of fluid, also its quantity and character, as in the peritoneum. Fluid in each pleura should be removed so as to prevent its flowing into the pericardium; or, in case the pericardium contains much fluid and any escape into the pleura, its quantity may be accurately estimated. The fluid in each cavity should be measured, and the quantity made a part of the record. Adhesions should be looked for and described. The mediastinal tissues, the relation of cysts, new growths, and aneurysms to adjacent viscera, and also the thymus may now be investigated. The last-named structure atrophies in childhood, but in infancy is an organ that should always be examined. The pericardium should now be opened by an incision extending from base to apex in a line parallel to the long axis of the heart. In opening the pericardium the writer has seen the heart injured so often that he desires to insert a word of caution and give a little more detailed method for preventing this accident. The pericardium is picked up in a fold either by the index- and fore-finger of the left hand or by the use of "rat-toothed" forceps; by gentle traction this fold of the pericardium can be raised to a distance of 2.5 cm The back of the knife is now placed against the heart and the fold

made as previously directed, is transfixed and the opening completed by cutting from within outward. A similar incision has been long recommended by surgeons while operating upon hernia where wounding the underlying tissue may be attended by calamitous consequences, and if applied to the pericardium with but slight precaution, wounding of the heart may be entirely avoided. From this incision, which is two or three centimeters in length, the incision in the long axis of the heart, as previously directed, may be readily made. Incisions at

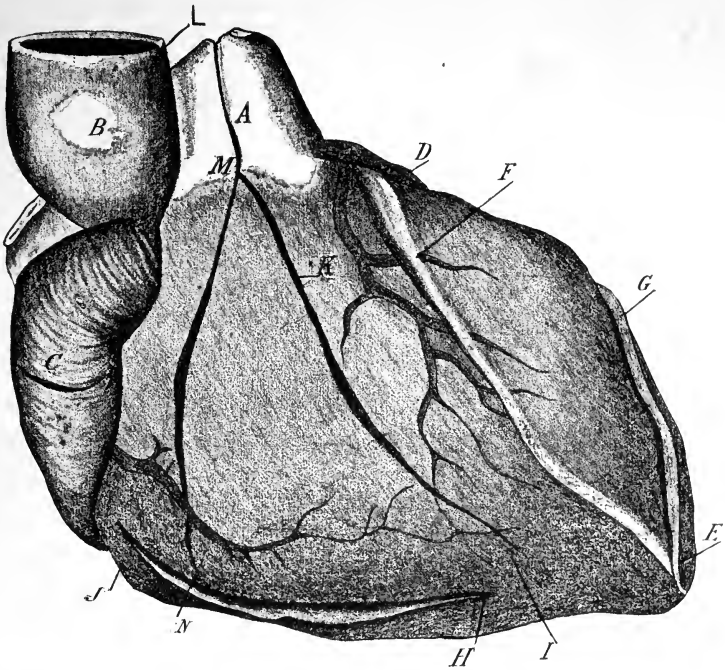

Fig. 7.—Heart Showing the Lines for Incisions in the Preliminary Examination and Final Section Fully Exposing the Valves.—(*After Virchow.*)

A. Pulmonary artery. *B*. Aorta. *C*. Right auricle. The incision *M* to *N* is that advised by Virchow. The one preferred by the writer is from *K* to *I*, for the preliminary opening of the right ventricle. The preliminary opening of the right auricle is made at *C*. The preliminary opening of the left auricle is made at *D*. The preliminary opening of the left ventricle is made at *F* to *E*. After the heart is removed, the incision made at *C* is carried out through the vena cava; the incision from *K* to *I* is carried through the pulmonary artery between the letters *M* and *A*, and below is carried around by *H* to *J*. The incision *M* to *N* is not made. The incision *F* to *E*, in the left ventricle, is carried around behind the pulmonary artery, *A*, and comes out in the aorta at *L*. From the lower portion, at *E*, the incision is carried upward to about where the letter *G* is shown this permits the flap to be turned back so that the mitral valve may be examined; the incision made may then be carried through the mitral orifice.

right angles to the long incision are rarely, if ever, demanded; the writer does not recall an instance in which he has needed a larger incision than that afforded by the opening extending from the apex to the great vessels. Examine the layers of the pericardium for evidences of inflammation, and look carefully for adhesions, particularly about the great blood-vessels. Measure the pericardial fluid and note its character.

The Heart.—Note the condition of contraction or relaxation of the

heart's wall; open the heart *in situ;* raise the organ by its apex, pass the fingers of the left hand under the organ, and so grasp it that the thumb and first finger will close the auriculoventricular orifice of the right side, and then make an incision into the auricle between the venæ cavæ. Examine and note character of contents; without relaxing the grasp on the auriculoventricular orifice, open the right ventricle by an incision in line with the pulmonary artery and close to the ventricular septum; insert the index-finger of the right hand and examine the contents The left heart is opened by grasping it as in opening the right. The auricle is incised near the appendix and immediately above the auriculoventricular septum, and its contents are noted. The left ventricle is opened by an incision almost parallel to

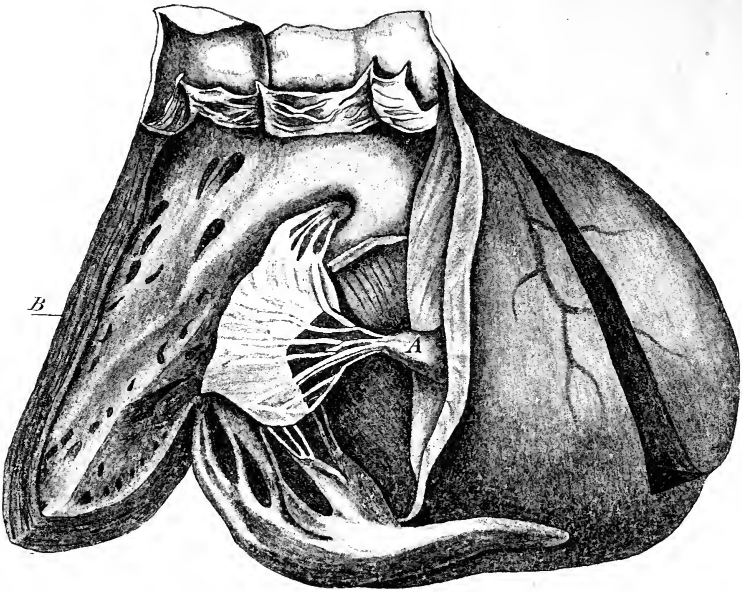

FIG. 8.—HEART SHOWING THE INTERIOR OF THE RIGHT VENTRICLE AND PULMONARY ARTERY.—(*After Virchow.*) If the incision *M* to *I*, figure 6, be made as advised by the writer, the papillary muscle (*A*) will be carried over with the ventricular wall (*B*), thereby better exposing the auriculoventricular orifice.

the opening made in the right ventricle, but on the opposite side of the septum, and the incision is directed toward the aorta. The presence or absence of blood or clots in the left ventricle must be carefully noted. Examine the great vessels as to abnormality, aneurysm, or other disease discernible externally; gross lesions involving the large vessel trunks, congenital defects, and the presence of thrombi or emboli had best be determined before the heart is removed; and if present, it may be expedient to complete the dissection before removing the organ. The heart, whether normal or not, should never be severed from abnormal or diseased vessels when the morbid condition is likely to have materially influenced the organ; this is especially true of malformations and aneurysms. When the relation of abnormality of the

intrathoracic vascular system to the air-passages or lungs is important, Letulle's method, mentioned below, should be followed. In the new-born it may be advisable at this time to trace the pulmonary artery and aorta, demonstrating the relation of one to the other, and the condition of the ductus arteriosus. Remove the heart, dividing the great vessels from below upward, severing the aorta last. Test the valves as to competency, being sure to wash out all clots before making the test. Enlarge the incisions already made so as to be able to examine the endocardium in detail. Carry the incision in the right auricle out through the two cavæ; prolong the incision in the right

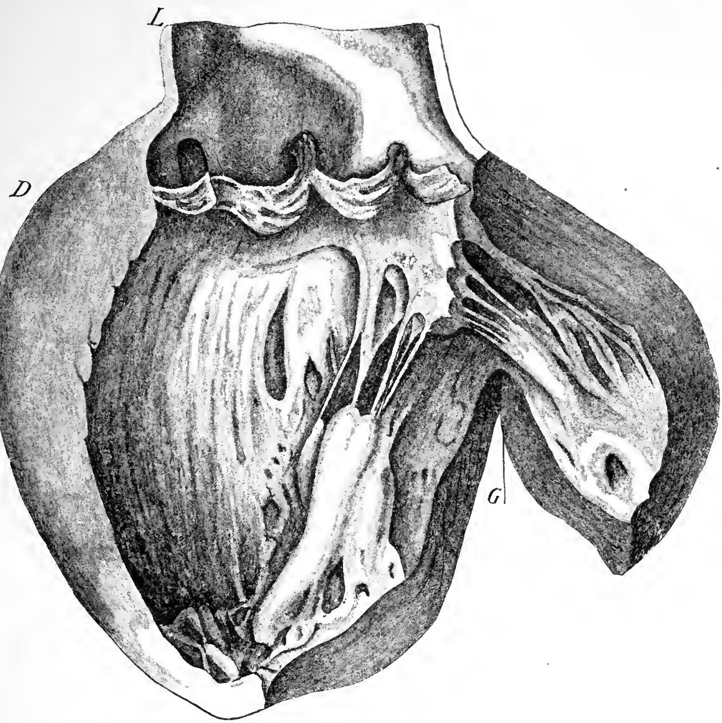

FIG. 9.—HEART WITH THE LEFT VENTRICLE LAID OPEN, SHOWING THE AORTIC CUSPS AND THE VENTRICULAR ASPECT OF THE MITRAL VALVE.—(*After Virchow.*)
The letters have the same significance as in figure 7.

ventricle through the pulmonary artery and the incision in the left ventricle through the aorta. The left auricle is opened by continuing the incision already made into the pulmonary vein. Note any vegetations on the valves, thickenings or opacity of the endocardium; examine closely the condition of the foramen ovale. State the general appearance of the cardiac muscle.

Measuring the Orifices: Graduated cones, balls of different sizes, and other devices for measuring the cardiac orifices can be purchased and by some are recommended; I have never held them in favor, as

the question of how much force may be used, or exactly where the reading is to be taken, can not be accurately answered; if the wall of an orifice be dense and unyielding—which normally it never is—such appliances might be of use. Ordinarily it is best to open the orifice and, without any lateral stress, lay a flexible tape over the exposed line; when such a tape is not available, a string, or better a wire, may be used and later measured; the circumference so obtained may readily be converted into diameter by dividing by 3.14.

Examine coronary arteries by passing a director into each in turn, and, with knife or scissors, opening the artery as far as possible. Probe-pointed scissors may be used to advantage, and if the probe-pointed blade is small, the arteries may be opened even to their smaller branches. Weigh the heart.

Both lungs may be removed at once. Adhesions must be carefully broken up; this can usually be accomplished by the fingers alone; occasionally, however, the knife or scissors (preferably the latter) will be necessary; when the adhesions are very dense or extensive, the costal pleura may be separated from the ribs and intercostal muscles. If the organs are adherent to the diaphragm, it is best to detach the latter from the ribs and remove it with the lung; often only a patch will require removal, at other times the entire diaphragmatic pleura may be adherent. Incise the great vessels as they pass out of the thorax; cut through the trachea, being careful not to injure the esophagus. Gentle protracted traction will strip the organs from the tissue behind bringing forward with the pericardium the aorta, which must be severed at the diaphragm. If it is desired to leave the aorta, this can easily be done by separating it from the pericardial attachments before delivering the lungs. When removed singly, the left lung is removed first; loosen all adhesions, pull the apex downward and the remainder forward, cutting the bronchi and vessels from behind; some workers prefer an anterior incision; probably the height of the operator or of the table leads to different methods and may influence the selection made by the beginner. Note the quality and quantity of any fluid flowing from the severed bronchus. Note the general appearance, color, and condition of the lung. Examine for crepitation, allowing the borders and margins to slip gently between the fingers and thumb; avoid force. At this time lay the lung on a solid surface, preferably slate or stone, or on one of the

Fig. 10.—Scissors.

Those shown in the upper cut will be most useful, particularly if the blade shown in the cut as having the sharper point be slightly probe-pointed.

limbs of the cadaver, to avoid any sounding-board influence, and carefully percuss the organ, comparing the result of percussion with the sensations elicited by palpation. The incisions made in the lung should be conspicuous by reason of their length, and the longer, other things being equal, the better. To accomplish this, it is best to use a long section knife (Fig. 14), which should be exceptionally sharp, making an incision from apex to base, extending through all the lobes in a line corresponding, as nearly as possible, to the axillary aspect of the organ. Lay open and dissect down the bronchi, and carefully examine their condition, a sharp lookout being maintained for the presence of foreign bodies. The branches of the pulmonary vessels should be examined for thrombi, emboli, and the presence of sclerosis. Note the appearance of the peribronchial glands. Weigh each lung separately.

Larynx, Trachea, Bronchi, and Thyroid Gland.—The examination of these structures is usually best accomplished after their removal *en masse*, together with the contents of the floor of the mouth and the pharyngeal wall. If the primary incision was carried to the chin the organs may easily be extracted; on the other hand, if they must be removed subcutaneously, considerable difficulty will be encountered. The skin must be carefully dissected from the underlying tissues, and a long-bladed knife passed from below upward, entering the floor of the mouth as far anteriorly as possible. making an incision laterally on both

FIG. 11.—GROOVED DIRECTOR.
Useful for opening arteries, tracing sinuses, ducts, etc.

sides along the rami of the lower jaw. The mouth is then opened widely, and the incision carried backward and upward, detaching the soft palate from the hard palate, and at the same time freeing the tonsils. The removal of this mass is accomplished by pulling the esophagus and larynx downward, pushing a long-bladed knife up behind the esophagus, and severing posteriorly and laterally the pharyngeal wall as high as possible. After removal the esophagus may be dissected from the larynx, and examined later, with or after the stomach, or it may be at once severed near the diaphragmatic opening, a ligature being applied to prevent the escape of the stomach-contents. If removed with the adjacent structures, it is opened on the posterior aspect, the larynx and trachea being opened anteriorly.

ABDOMINAL VISCERA.—The *spleen* is now removed. This is accomplished by gently lifting the organ out of its normal bed, pulling it forward, and severing the blood-vessels close to the hilum. As a result of past peritoneal inflammation, diaphragmatic pleurisy, or inflammation of some adjacent viscus or tissue, as the colon or perirenal structures, the spleen may be anchored by firm adhesions of its capsule to contiguous viscera. Under such circumstances it is best to dissect the organ out with very great care, as protracted or violent traction may rupture the thin capsule; and if it be softened as a result of infectious diseases or other cause, the entire splenic pulp may be forced through a compara-

tively small opening in the capsule of the organ. Its general appearance described, make one long incision through the convexity extending down to the hilum. Note color and consistency of parenchyma, prominence of the Malpighian bodies, and stroma. Weigh the organ.

The Kidneys.—Ascertain whether both are in their normal positions, if possible. The left suprarenal body and left kidney are next examined. As a rule, the adrenal and corresponding kidney may be removed together. This can readily be done by incising or tearing the peritoneum along the upper and posterior border of the kidney and gently dissecting with the fingers the connective tissue holding the adrenal in place. Raise the kidney from its normal position, note condition of blood-vessels and incise them; examine ureter and sever it. With very little effort the ureter may be traced downward to the bladder. This should be done before severing the kidney, as later it may be quite impossible to demonstrate that the canal contained no obstruction. The perirenal fat should be carefully removed from the kidney and the surface of its capsule accurately described before incising it. Hold the kidney in the left hand, with the pelvis directed toward the palm, and with one sweep of a sharp knife incise, from the cortex to the pelvis, in the long axis of the organ. On section, note consistency, color, the relative proportion of cortex and pyramid (normal cortex equals one-half the pyramid); the condition of capsule, whether thickened, tense or flaccid, or adherent to cortex; also note appearance of stripped surface of cortex, whether smooth or rough, etc. Examine pelvis of kidney, and weigh the organ. The same process is repeated upon the opposite side.

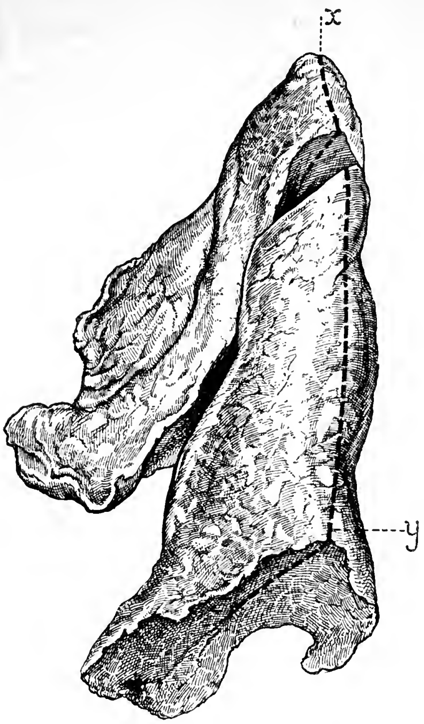

FIG. 12.—LINE OF INCISION THROUGH THE POSTERIOR BORDER OF THE LUNG.—(*Letulle.*)

This cut, following the line from x to y, should extend to the hilum. The surfaces exposed by the foregoing method are further incised at short intervals.

Examine *bladder and internal genitals.* The technic of this examination depends largely upon the conditions present. When the examination of the upper urinary tract (kidney and ureter) has led to any suspicion of disease, it is best not to detach the kidney from the ureter or ureter from the bladder until the examination has been completed. The examination of the pelvic viscera can usually best be accomplished after evisceration of the pelvis. It is best, however, to open the bladder and examine its contents before eviscerating, and in the female, when

there is any question of criminal abortion, a thorough examination should be made by finger and speculum, using no cutting or probe-pointed instrument of any kind until wounds have been excluded—as far as it is possible—before the examination is completed. Evisceration of the pelvis is best accomplished by an incision anteriorly, under the pubic arch, hugging the true pelvis posteriorly, and removing the rectum with the other contents of the pelvis. The testicle may be removed without any external incision in the scrotum by simply dissecting the skin anteriorly from the pubes and pulling the testicle by the spermatic cord gently up into the wound, from which it may be removed, if necessary dissecting the cord around to the seminal vesicles. The penis may be simply retracted through the floor of the pelvis, and removed with the prostate and bladder.

The removal of these organs without the full consent of the deceased's family should never be made, as the excision of the genital organs is always looked upon as having been done merely to gratify morbid curiosity, and exactly why it is always discovered seems very hard to determine; the fact remains that the uninitiated have been severely censured for the removal of the external genitalia, even in cases where it was perfectly justified by the findings and where it was necessary to exclude other possibilities.

FIG. 13.—INCISION FOR SEPARATING THE ORAL AND PHARYNGEAL STRUCTURES FROM THE FLOOR OF THE MOUTH.—(*Letulle.*)

The rectum should be dissected from the posterior wall of the bladder in order to expose the prostate and seminal vesicles. In the female, as this is not necessary, the rectum is opened on its posterior aspect, the vagina laterally, and the urethra and bladder anteriorly, thus permitting all the parts to be restored to their normal relation with each other. The opening on the lateral aspect of the vagina is carried anteriorly at the upper end and continued through the anterior wall of the cervix and body of the uterus. If urine be present in the bladder, its character and quantity should be noted, and it should be preserved for future examination.

The left semilunar ganglion is examined, and any firmness or inflammatory signs noted. The ganglion should be preserved for microscopic examination. The corresponding organ of the right side is next in order of examination.

The Stomach and Duodenum.—In cases where poisoning is suspected, ligatures are applied at the cardiac extremity of the stomach and the upper end of the duodenum, and the organ removed; in order that the contents may be carefully examined, the stomach, without open-

ing, should be placed in a clean jar and sent to the chemist. In case it is decided to open the duodenum and stomach *in situ*, as is best when the question of poisoning does not enter into the case, make an incision along the anterior surface of the duodenum and greater curvature of the stomach. Examine contents, condition, and appearance of mucous membrane. Foreign bodies are frequently met with in the stomach. Determine if the bile-duct is patulous by pressing upon the gall-bladder and watching for the escape of bile. In case this simple procedure does not reveal the presence of the ampulla and

FIG. 14.—LONG, THIN, BRAIN KNIFE, OF VALUE FOR INCISING ORGANS.

Originally designed for brain dissection, but at present used for incising kidney, liver, spleen, tumors, etc. As shown in the illustration, the instrument should not have a cutting-edge measuring less than sixteen centimeters. The graduation along the back of the knife affords a convenient measure. On the other side the graduation is in inches.

demonstrate that the cystic and common ducts are patulous they should be carefully exposed. This can not be done after the removal of the pancreas, duodenum, or liver; as it is important in many, if not all, cases to assure one's self of the condition of the hepatic, cystic, and common ducts, and as cutting through either of them may render later demonstration unsatisfactory or even quite impossible, they should, therefore, be dissected out *in situ*. Open the ductus communis choledochus, examine mucous membrane, and continue the incision upward into the gall-bladder and larger hepatic ducts.

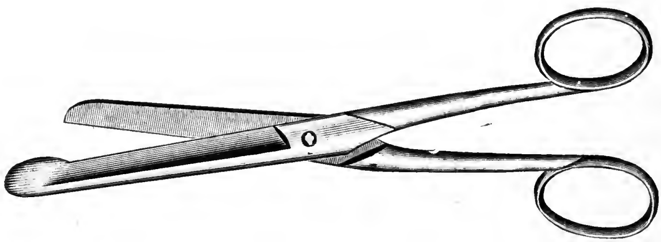

FIG. 15.—ENTEROTOME.

Useful for opening stomach, duodenum, intestines, etc. Not uncommonly the blunt-pointed lower blade is so made that it forms a tooth, like the barb on a fish-hook, and when introduced, can not be withdrawn. Such hook-pointed enterotomes are to be avoided.

The portal vein, hepatic vein, and vena cava may be opened before the removal of the liver; or, as the first two must be severed during the removal of the organ, they may be examined at that time. The condition of their contents and appearances of their walls must be noted.

The *liver* may now be detached from the diaphragm, or, if it is adherent to that structure, the two may be removed together; when the lung, liver, and diaphragm are fused by adhesions at their points of contact, and when there may be any suspicion of a suppurative lesion burrowing in either direction, it is best to let the lung remain

in situ until the proper time for examining the liver, when the three structures can be removed together; neither the lung nor the liver should be sacrificed, but only that part of the diaphragm immediately involved need be removed with the attached viscera. The shape and color of the liver and any deformities of the lobes should be noticed, the anterior margin examined, and its condition recorded. The incision made to disclose the interior of the liver should be a long, sweeping cut, on the superior aspect of the organ, extending through the longest axis, including both right and left lobes and sufficiently deep to permit the folding of the two parts without tearing the narrow band of tissue holding them together on the inferior surface of the organ. On section, the firmness or resistance should be noted; also the color, whether uniform or mottled, and whether or not bile staining be present. Weigh the organ.

Pancreas.—At the time the bile-passages are opened down to and through the ampulla, it is well to seek the duct of Wirsung, and, if possible, the extension into the pancreas; accessory ducts should be sought. As the head of the pancreas is dissected from the duodenum a careful lookout should be maintained for any additional, as well as normal, ducts. Separation of the pancreas from the duodenum, which it occasionally envelops, is often extremely tedious. Aberrant pancreatic tissue should be sought in the stomach, duodenum, and jejunum. The tail and most of the body of the pancreas may be detached and

FIG. 16.—PROBES.
These should be at least fifteen or twenty centimeters long. One should be very slender.

transversely incised partly through, at short intervals (1 to 2 cm.), beginning at the splenic end. Careful inspection of the surface exposed at each incision commonly discloses the larger duct about the junction of the body and head of the organ. As soon as recognized it may be explored by a fine probe and finally opened.

The *esophagus* should next be examined.

Intestines.—A better view of the other organs and greater working room are afforded by removing the intestines immediately after the spleen. The rectum is ligated just below the sigmoid and the latter separated by incising the mesosigmoid close to the bowel. The presence or absence of renal mobility should be determined, after which the colon, descending, transverse, and ascending, is detached in the order named. The caput coli is raised from its bed, the appendix detached from any adhesions, and removal of the small intestine continued by sectioning the mesentery as close as possible to the gut. As the different parts of the ileum come in view any abnormality in color, evidence of inflammation, dilatation, or narrowing should lead to a closer examination of the mesentery, which ordinarily is inspected at this time. While dividing the mesentery watch for enlarged glands, cysts (chylous), tumors, thrombosed vessels, fat necrosis, etc. When the blood or chylous vessels are abnormal, it may be well to remove these with, and leave them attached to, the intestine. Should thrombi,

or other lesions involving the vessels, be disclosed, the veins and arteries should be dissected to the main trunks, and if possible the cause, if local, determined before going further. Any lesion located in the mesentery and influencing the intestine should be traced with that structure to which it had best be left attached. The gut should be carefully opened, and the contents examined as the incision in its wall is gradually extended. After the incision made by the enterotome has been concluded the mucous surface should be gently washed by a slowly flowing stream of water, and examined for inflammation, ulcers, cicatrices, perforations, constrictions, etc. It is best to open the intestine before washing it out, in order more accurately to determine the contents, examine for animal parasites, locate foreign bodies, etc., but cleanliness and convenience often lead to an unwise reversal of the proper order. In cases of suspected poisoning the unopened intestine should be sent, in a clean jar, to the chemist.

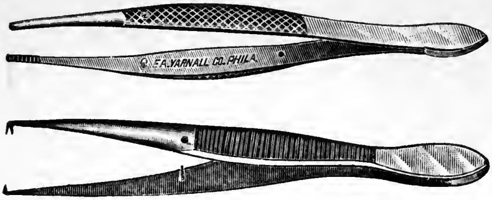

Fig. 17.—Dissecting Forceps.
One of these should be toothed. These will be needed in the finer dissections, as in tracing the hepatic duct, portal vein, and receptaculum chyli.

The *thoracic duct* should now be traced, and the *retroperitoneal glands* and *receptaculum chyli* examined.

The *aorta* and its branches may now be examined in detail.

The Head.[1]—Insert the scalpel, with its back toward the skull, just behind one ear, and carry an incision across the vertex, cutting from within outward. If the knife is not too sharp, the hair may be parted and

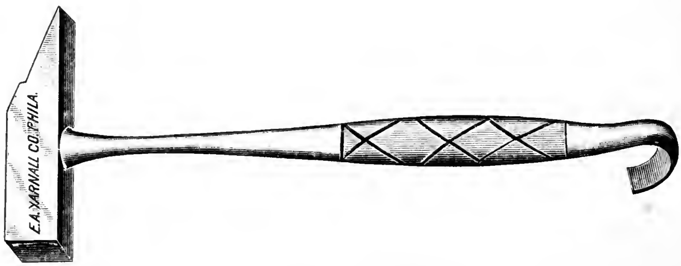

Fig. 18.—Mallet or Hammer.

thrown backward and forward as the hand and knife are withdrawn. The incision should be far enough back to be invisible from the front when closed. The scalp is reflected forward and backward from this incision as low as the superciliary ridge in front and the occipital protuberance behind.

In many cases great care must be used to avoid a tear at or

[1] See article by Buhlig on general and special methods for examining the brain and spinal cord; "Cleveland Medical Jour.," Jan., 1904, p. 28.

around the ear, as tension is produced by pulling the anterior and posterior scalp-flaps down; to avoid this unsightly tear, which may run down in front of the ear, insert the knife under the skin, in the incision already made, just behind the ear, and dissect the skin free from the deeper structures behind and in front of the ear. The scalp-flaps, as already described, do not include the temporal fascia or muscle, both of which are now cut through and reflected in the line of the contemplated saw-cut. All soft tissues should be incised and pushed out of the way of the saw, otherwise they pack the teeth of the instrument and greatly impede sawing. When the skull-cap is replaced, the fascia and the muscles may be sewed together, thereby securing the bone in place—a matter of great importance in private postmortems when the body is to be exposed at a funeral or to friends.

Inspect the skull for evidence of injury or disease. In opening the skull there are three methods of procedure—one should never be used when it can be avoided, one may be used in a few cases, and one is applicable in the vast majority of instances: (1) The "undertaker's cut" is made by sawing across the forehead just back of the hair line, from one temporal fossa to the other, and carrying a second saw-cut around the posterior base, parallel with the base line, joining the anterior cut in each temple. This method does not permit of satisfactory removal of the brain. (2) The second method should always be used in medicolegal cases, and whenever the question of fracture may arise. It does not demand the use of a chisel, and affords abundant opportunity for examining the interior of the skull. A circumferential line is drawn around the skull, on a level with the superciliary ridge in front and the occipital protuberance posteriorly, and the skull sawed through at this line. (3) The third method, and the one most commonly employed, consists of a V-shaped incision; as viewed laterally, the anterior arm of the V is parallel with the base of the skull, on a level with the superciliary ridge, and extends backward 1 cm. behind the external auditory meatus. The other arm of the saw-cut passes obliquely across the vertex just back of the incision already made in the scalp. It may be necessary to break out the angles of the saw-cut with a chisel; care must be used not to mutilate the ear in making the saw-cut. The adjustment and retention of the calvaria in place may be further aided by making the posterior saw-cut also V-shaped. The angular junction of the two lines which form the V is directed upward, something like the occipitoparietal

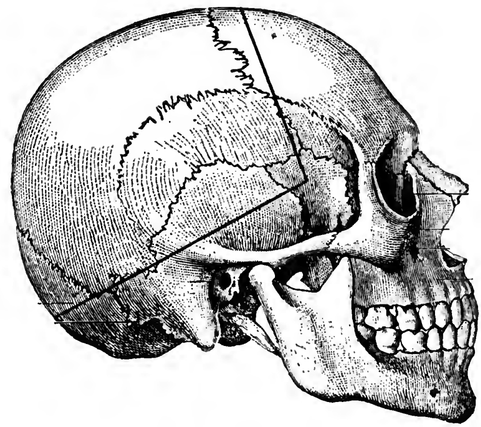

Fig. 19.—Heavy Line Indicating Course Taken by Saw-cut in So-called Undertaker's Method.

It is possib e that the base line as drawn in this illustration is too low however, this is immaterial, as the method is under all circumstances to be avoided.

suture. To repeat: This makes two V-shaped saw-cuts as follows: Viewed laterally, the anterior arm of the first V is parallel with the base line, and extends from the superciliary ridge to just behind and above the external auditory meatus, the posterior arm of this V being subdivided into the two arms of a second V, which, as viewed from behind, is upside down. The advantage of this incision lies in the easily adjusted calvaria, the wedge-shaped cap being readily replaced and secured in position, so that no external evidence of the postmortem will be visible when the scalp is returned to place and sutured.

Inspect the interior of the calvaria for evidence of injury or disease, noting its thickness and the condition of the diploe and of the external and internal tables. The dura may be removed, or, rather, reflected back, by incising it along the lower saw-cut and detaching the falx cerebri from the crista galli. When, as in the very young, the dura must be removed with the calvaria, it is necessary to incise that membrane along the line of the saw-cut, and to sever the falx anteriorly and posteriorly before making any attempt to raise the skull-cap.

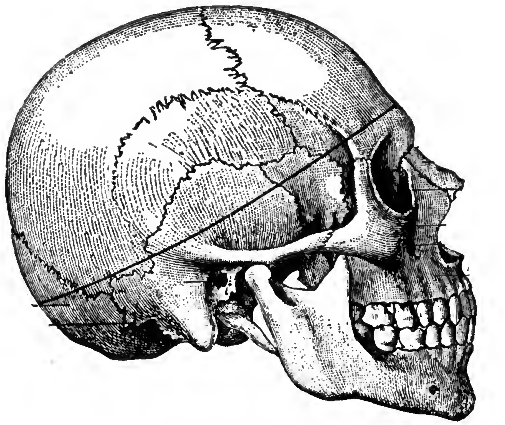

FIG. 20.—CIRCUMFERENTIAL SAW-CUT, TO BE PREFERRED IN ALL MEDICOLEGAL CASES.
The exact location of the line will vary slightly, depending upon the conformation of the skull. It is usually about as indicated above.

Inspect the surface of the brain for superficial injuries or disease, but make no incision into it. It may here be necessary to note the relation of brain landmarks to the skull, fixed points of the latter being selected for the comparison.

The brain is next to be removed, beginning in front by carefully raising it from the base, being sure to raise the olfactory bulbs with the hemispheres; still cautiously elevating the hemispheres, sever the nerves as they pass out of the skull, those in front first, and then in order as they appear. When the tentorium is reached, detach it from the temporal bone and follow the base, severing the nerves as they find exit from the posterior fossa; lastly, pass a long, slender-bladed knife along the basilar process of the occipital bone, and down into the spinal canal, cutting the cord as low as possible. In order to section the cord as nearly transversely as possible and to avoid the oblique incision made in the manner just directed, some operators prefer the use of a myelotome. After section of the cord the entire brain can be easily removed. Complete the examination of the interior of the skull, noting the condition of the bone, blood-vessels, sinuses, etc., dissecting the dura from the base to facilitate the examination of the bone. Before detaching the dura the contained sinuses should be opened and examined for evidences of thrombi, septic processes, etc. The posterior part of the orbit and the

eyeball may be examined by chiseling the roof; in the same way examine the frontal, sphenoid, mastoid, and ethmoid sinuses and the internal ear.[1] The *brain* should be, in most instances, hardened before dissection; if this can not be done, immediate examination may be made as follows: Make a careful examination of the meninges, and note the color, consistency, etc., of the external surfaces, including the base; the consistency is best determined by gently palpating the entire cortex. Examine the blood-vessels at the base, tracing them into the brain-tissue. An incision is made on each side, just over the corpus callosum, into the lateral ventricles, and continued backward and forward, that they may be carefully inspected; the amount and character of the fluid present are noted. The lateral ventricles are joined by an incision through the fornix, reflecting the corpus callosum backward, exposing the tissues beneath. Search for hemorrhages, areas of softening, tumors, inflammation, abscesses, etc. Lateral incisions are now made in the cortex from the ventricle outward, so as to note the condition of the cerebral substance; the incisions should be parallel, not over one centimeter apart, and the membranes should not be cut through, as they will retain the cut parts in position. The brain is then turned over, and the tissue of the base examined by transverse incisions through the medulla, cerebellum, etc., examining for such changes as previously noted. Weigh the brain.

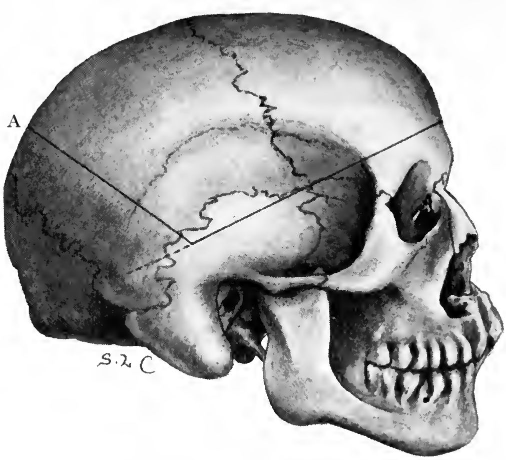

FIG. 21.—WEDGE-SHAPED CALVARIA REMOVED BY THE LINE OF SAW-CUT RECOMMENDED. (See Text.)

If the posterior cut is so made, from the right and left sides, that the point just above the letter A is the apex of a triangle, two sides of which are formed by posterolateral saw-cuts, there will be no difficulty in retaining the wedge-shaped calvaria in place.

While occasionally much information can be obtained by the gross examination of a freshly removed brain, improvements in histologic technic have made the microscopic examination of greater importance. In order to obtain valuable information from this method, it is necessary to secure sections which permit reconstruction of the organ, so that the connection between different parts may be traced. This implies the use of some serial method similar to that employed in embryologic work. The size of the human brain precludes satisfactory serial sections of the entire mass, and as the serial sections are for the purpose of demonstrating histologic lesions in paths or bundles, each case will become to a certain extent a law unto itself. In the interest of complete neurologic investigation the pathologist must forego the satisfaction of immediate results from dissection of the fresh brain.

[1] Schalle ("Virchow's Archiv," Bd. lxxi, p. 206) gives details of a method for examining the organs at the base of the skull, using a chain saw.

It is desirable to harden it in formaldehyde-water (formalin 10 parts, water 90 parts) for several days before making any incisions except those through the margins of the corpus callosum into each lateral ventricle, which are preliminary to all methods of dealing with the brain, and are simply to promote hardening of its interior. If, however, incisions are to be made at once, the pathologist should consider, in relation to any gross lesion present, the direction of tracts which

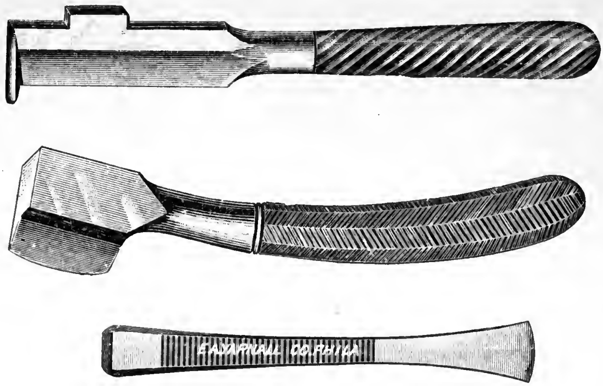

FIG. 22.—CHISELS.
If only one is to be purchased, the lowest one will be of most use.

may be degenerated. Such tracts should be cut at right angles to their course in order that the sections may be used for microscopic study. In this point of view the conventional methods of Virchow and of Pitres are objectionable. The safest single incision is Déjérine's horizontal cut passing through the cerebrum at a level slightly beneath the upper surface of the callosum. This transects the basal ganglia and the internal capsule at their widest parts, and will usually reveal any gross lesion. If this is not conclusive, another section may

FIG 23.—MYELOTOME.
Used for separating the brain from the spinal cord. The advantage claimed for this instrument is the facility with which the cord may be cut transversely, thereby avoiding the objectionable oblique incision which is usually secured when the ordinary knife is used for the same purpose.

be made 1 cm. lower than the first and parallel to it. A section lengthwise of the optic tracts will show their connection with the primary optic centers, and at the same time the nuclei and fibers of the third nerves.

To reserve the remainder of the brain-stem for microscopic study of its nuclei and nerve-roots, the most advantageous section is a transverse one in the upper half of the pons; that is, above the fifth nerves, which are about half-way down the pons. Above all to be avoided

are longitudinal bisections of the brain-stem. For the study of nerve-cell bodies and of neuroglia small portions of the fresh tissue, removed from the particular centers of the cortex, and from the cervical and lumbar cord, are put at once into the special fixatives. For Marchi and Weigert preparations and for nuclear and general staining, the bulk of the brain and cord may be placed in Müller's fluid, or in Orth's mixture for twenty-four to forty-eight hours, followed by Müller's fluid.[1]

The Pitres-Nothnagel Method.—The lateral ventricles are opened as described; the pons and cerebellum are severed by section of the peduncles; the cerebrum is divided by a vertical section (longitudinal) through the median line—the third ventricle; each half of the cerebrum is then incised from above downward, transversely to its long axis and as nearly as may be parallel with the fissure of Rolando: (1) Five centimeters in front of fissure of Rolando; (2) through posterior margin of the frontal convolutions; (3) through ascending frontal convolution; (4) through ascending parietal convolution; (5) three centimeters posterior to fissure of Rolando; (6) one centimeter in front of parieto-occipital sulcus.

The fixation of each of these sections completed, serial sections are made from each area. While much more tedious and requiring greater care, this method permits of reconstruction and the adaptation of parts so as to follow fillets, or paths, with a precision not possible by the cruder methods.

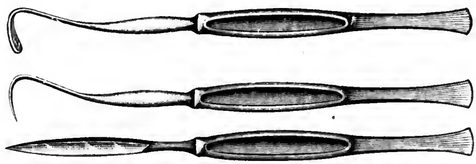

FIG. 24.—SCALPEL WITH BLADE SHAPED SOMEWHAT LIKE A BISTOURY.

Useful in removing the brain and spinal cord. The aneurysm needle and tenaculum shown are useful at times, but are not essential.

For demonstrating the condition of the blood-vessels at the sacrifice of everything else, the brain may be gently washed away and the blood-vessels floated out in a basin of water.

THE SPINAL CORD.—The body is turned upon the abdomen, and blocks are so arranged as to arch the vertebral column. As this procedure may cause leakage of fluids in a body already opened anteriorly, it may be best, in private postmortems, to examine the cord first; after the body is turned on the back, little if any fluid should escape through a properly closed posterior incision. An incision is then made through the skin, over the spinous processes, extending from the occiput to the sacrum, and the muscles, fasciæ, etc., detached from the vertebræ so as to expose the laminæ on both sides. These are then sawed through, the saw being held parallel with the spinous processes and near the junction of the laminæ and pedicles. The section extends from the second vertebra to the sacrum. The excised strip is now removed, the chisel or bone-cutting forceps being used as aids if necessary.[2] Inspect the meninges and remove these with the cord, carefully detaching, with a sharp knife, the nerve-roots as they

[1] For formulas see chapter on Histologic Technic.

[2] Chavigny ("La Presse Médicale," July 20, 1904, p. 460) describes an ingenious lever device for removing the spinous processes and laminæ. I have never used it, but Letulle writes me that it is a useful appliance.

pass out of the canal. The lower end of the cord, with its membranes, is first detached, and the removal continued from below upward. During the removal of the cord, whatever traction may be necessary should be made on the *meninges only*, and traction on, or crushing of, the cord should be carefully avoided. After removal of the cord examine bodies of vertebræ; dissect out and preserve a number of the intervertebral ganglia. Open the dura in the median line posteriorly and examine the cord by making transverse incisions one to two centimeters apart.

The examination of the *joints* and *bones* of the skeleton may have preceded the visceral examination, but ordinarily it is deferred until that has been completed. Sometimes it is desirable to obtain bone-marrow without fracturing or otherwise severing the continuity of the bone. This is best accomplished by two saw-cuts parallel, four or five centimeters apart, and extending a little over half-way through the bone; by means of a chisel this block of bone is split out, bringing with it the marrow. A block of wood may be slipped into the space occupied by the piece of bone removed, and, where this fits tightly, bringing the tissues together over it will usually prevent the occurrence of a fracture during the ordinary handling of the body.

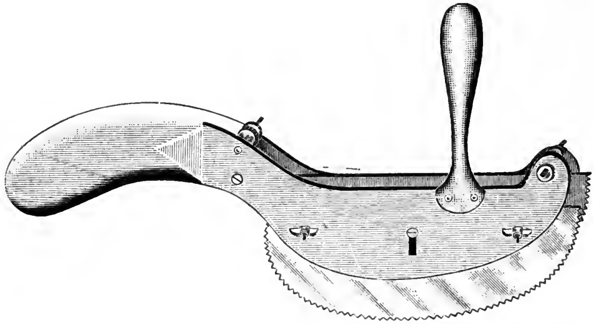

Fig. 25.—Double Saw (Rachiotome) for Sawing through the Laminæ of Both Sides at Once. It saves time and labor, but equally good work can be done without it.

The removal of the salivary glands is not often demanded. The sublingual and submaxillary glands may ordinarily be removed by the method already described when considering the larynx and pharynx. A portion of the parotid gland can sometimes be removed by dissecting the skin down from the temporal region anteriorly, and below the incision already advised for exposing the skull.

By *Letulle's method*[1] the neck and the thoracic and abdominal cavities are eviscerated *en masse* and the subsequent examination of the organs begun and to a large degree completed while they are still attached together. To accomplish this, the preliminary incisions, including opening the abdominal cavity, are those for which directions have already been given (pp. 7 to 9). A long knife is passed upward through the floor of the mouth, separating the tissues from the inner surface of the inferior maxilla; the uvula and palatine arches are freed from

[1] I have taken some minor liberties with Letulle's plan, which to one having a thorough knowledge of anatomy and some experience in postmortem work, I think can be strongly recommended.

their osseous attachments. The posterior wall of the pharynx is detached from the subjacent bone and pulled downward. The large arterial trunks in the neck and the subclavian vessels are divided; the entire mass is now pulled downward, the section being made close to the vertebræ until the diaphragm is reached. This structure is incised along the ribs and vertebræ, and by keeping close to the posterior abdominal wall, the evisceration is completed. When the floor of the pelvis is reached, the incision in the male differs from that used in the female. In the former the bladder is dissected from the anterior abdominal wall and pubis, after which a long knife is thrust downward under the pubic bone, and, with the scrotum pulled upward, is made to emerge at the perineoscrotal margin near the median line, from which point it is carried around the sides of the pelvic outlet in such a manner as to remove anus and pelvic floor; where permissible, the penis and testes may be retracted and removed with the mass. In America, at least, this excision of the external genitalia will rarely be permitted, and hence the incision had best pass through the bulbous portion of the urethra, allowing that structure to be removed with the bladder, rectum, and other viscera. In the female the knife, thrust down from above, emerges at the side of the vulva and is carried around the anus, similar incisions being made on either side; the two incisions are joined above the vulva and the dissection from the pubic bone completed. The umbilical attachments should be severed before evisceration is begun; in the infant it is well to cut around and excise the umbilicus and its vessels; this is not necessary in the adult.

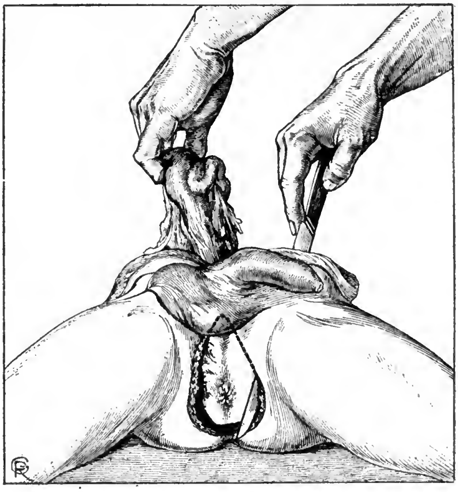

FIG. 26.—PERINEAL INCISION FOR REMOVING ANUS, BLADDER ETC., IN THE MALE.—(*Letulle.*)

The anterior relations of the organs may have been described before evisceration; usually this course is to be recommended. After removal the mass is laid upon its anterior surface and the examination continued in the following order: (1) Large and small azygos veins. (2) The thoracic duct, including the receptaculum; the former is detached throughout its extent from the receptaculum to its junction with the vein. (3) Examine and remove the adrenals. (4) Isolate the ureters. (5) Disengage the kidneys, exposing the arteries and veins which, after examination, should be sectioned, using care not to wound the pelvis or ureter. The kidneys are then laid down on either side, the ureteral connections with the bladder being maintained. (6) Open the abdominal and thoracic aorta from the iliac vessels upward. (7) Open the vena cava. (8) Raise and pull to one side the

abdominal aorta and cava, exposing the trunk of the portal vein and its larger branches, and open them. (9) Expose the common duct, dissecting upward to the cystic and hepatic ducts, which should also be brought into view. (10) Expose the posterior surface of the pancreas, which may now be examined; the organ, however, should not be detached from the duodenum until examination of the intestine has been completed. (11) The aorta is cut transversely at the level of the renal arteries and dissected upward to the arch. (12) Raise the esophagus near its middle, dissecting downward to the cardia and upward to the pharynx. (13) Examine the organs from the mouth and pharynx, including the palate, tonsils, tongue, and sublingual glands. (14) Separate the upper attachments of the esophagus, which may be ligated at its upper or lower end, whichever in a given case seems desirable. (15) Examine the epiglottis and open the larynx; at this time the laryngeal nerves may be dissected. (16) Examine and open the trachea and primitive bronchi by continuing downward the incision already made in the larynx. (17) Expose and examine the pulmonary pedicle, not incising the vessels, which are opened later. (18) Free the cervico-thoracic portion of the pneumogastric nerve. (19) The lymph-nodes of the posterior part of the body. This completes the posterior examination. The mass is now turned over, being careful to retain the normal relations.

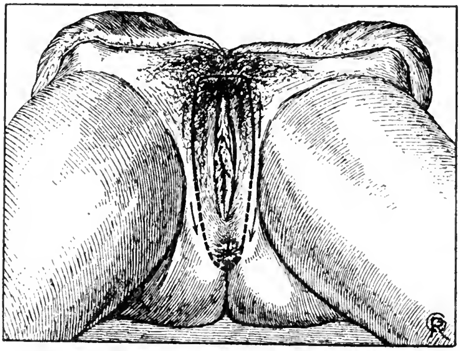

Fig. 27.—Perineal Incision for Removing the Rectum, Anus, and Reproductive Organs of the Female. —(*Letulle.*)

The examination of the organs from the anterior surface is conducted in the following order: (1) Examine and remove the thymus. (2) Isolate and remove the thyroid gland, noting its relation to the trachea and the presence or absence of a pyramidal lobe. The possibilities of aberrant masses of thyroid tissue should be borne in mind during the subsequent examination of the mediastinal structures. (3) Open the superior vena cava and its branches. (4) Examine the freshly opened veins for the mouth of the thoracic duct. (5) Open and inspect the pericardium. (6) Examine the cardiac plexus of nerves. (7) Examine the arch of the aorta, noting its relation to the pulmonary trunk and branches. Cut through the aorta at the cardiac end of the incision already made in the arch. (8) Expose and open the pulmonary trunk and branches to the entrance of the latter into the lung. (9) Expose and open the extrapulmonary part of the pulmonary veins. (10) Complete the examination of the pulmonary pedicle, examining the peribronchial glands, at which time the lungs may be separated, although usually this is done after the heart is removed. (11) External examination of the heart. (12) Cut the pulmonary arteries and aortic arch and finally the veins entering the auricles; remove the

heart. (13) Section the pulmonary pedicles and remove the lungs. (14) Complete examination of the diaphragm. (15) Examine the liver, gall-bladder, and cystic duct; excise the liver. (16) Remove the spleen. (17) Isolate and examine externally the stomach, duodenum, and pancreas, ligating the jejunum at its origin and bringing with the mass the already isolated esophagus. (18) Examine and remove the ileum and large intestine from above downward, essentially as already directed on page 19 (19) Complete the removal of the mass containing the esophagus, stomach, pancreas, and duodenum; open esophagus, stomach, and duodenum; examine relations of latter to pancreas; examine pancreatic ducts and complete examination of pancreas. (20) Complete the examination of the peritoneum, including the mesentery, etc. (21) Complete the examination of the urinary organs, including the kidneys, ureters, bladder, and urethra. (22) Examine (A) Prostate, seminal vesicles, testicles, and ducts, or (B) tubes, broad ligaments, ovaries, vulva, vagina, and uterus.

In order to make a **bacteriologic examination,**[1] a Bunsen burner, alcohol lamp, or other means of sterilizing the instruments used must be at hand. Cover-glasses, cover-glass forceps, platinum wire, various cul-

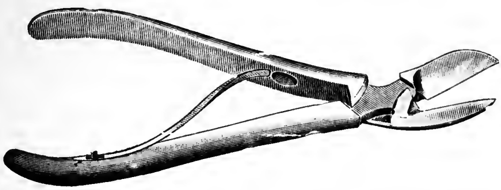

FIG. 28.—BONE-CUTTING FORCEPS.
These are not absolutely essential, but will be convenient. They should be long—not less than fifteen centimeters.

ture media, and labels will be needed. In order to secure material not contaminated by accident, it is necessary to enter all cavities through a previously sterilized field. The disinfection of the area is best accomplished by heat. In order to secure inoculations from the peritoneum, it will be necessary, as soon as the wound in the abdominal wall approaches the cavity, to sear the surface with a hot scalpel, or, what is better, a spatula; the searing must be thorough; through the seared surface, with instruments kept sterile by frequent passage through the flame, the wound is cautiously extended until the cavity is reached. At once inoculations and cover-glass spreads are made. In a like manner the pleura may be opened through an intercostal space. Inoculations from the interior of the pericardium are best obtained by cautiously searing the fold raised as already directed (p. 10), and puncturing with a hot knife or scissors. To secure blood from the heart, a part of the surface is sterilized by searing with a hot iron, or one of the great vessels may be similarly treated and opened, using for this purpose a hot knife or scissors. A platinum loop may then be thrust into the cavity, and inoculations and spreads made in the usual manner. As soon

[1] As to the value of bacteriologic examinations postmortem, see Chvostek and Egger ("Wien. klin. Woch.," 1897, x, 3), Achard and Phulpin ("Arch. de Méd. Exp.," vii, 1, p. 25), Simmonds ("Virchow's Archiv," 1904, Bd. 175, H. 3), Gradwohl ("Annales de l'Inst. Pasteur," Dec. 25, 1904, p. 767).

as the skull cap is removed the dura should be seared, punctured with a sterile knife or scissors, and cultures and spreads obtained from beneath.

Systematizing the Description.—In considering organs a definite field or plan should be adopted. Of course, this will be quite often varied, but it has the advantage of occupying no more time than any other method, and assures a systematic record which makes all postmortems comparable. The following is advised, although each worker will probably acquire a routine of his own: (1) *Malposition*, and, if out of place, is the malposition congenital or acquired, and what influence has it had on the position or function of other organs: *e. g.*, a misplaced right kidney may press upon the duodenum or bile-duct or upon both. After removal it is too late to determine such facts, which may be of the highest importance in explaining symptoms. (2) *Malformations.* (3) *Make measurements* of the organ and *weigh* it; as the organ can be weighed only after removal, and as the removal severs its connection with the body, note must be made of *color*, *consistency*, *density*, and *shape*,—the latter being outlined when the measurements are made,—and a full *description of its external appearance* must be given; at the time of severing its attachments the *fullness of the blood-vessels*, the presence or absence of *edema*, and, if it possesses a duct, the condition and contents of that structure, must all be recorded. Whatever observations are to be made with regard to the ducts of organs must be completed before severing their connections. These studies enable one, to a certain extent, to record the presence or absence of the following points, which come next in order: (4) *Atrophy*, including *hypoplasia* or *aplasia*. (5) *Hypertrophy*, including *hyperplasia*. (6) *Infiltration.* (7) *Degeneration.* (8) *Inflammations*, including acute *infections*. (9) *Lesions of systems: (a) vascular; (b) lymphatic; (c) nervous.* (10) *Chronic infections.* (11) *Tumors.* (12) *Parasites.* If the steps indicated be followed, but little will be overlooked.

Fig. 29.—Postmortem Needles. These should be eight to fifteen centimeters long and correspondingly heavy.

As soon as an organ is incised pieces should be removed and fixed for microscopic study; the records may be completed after the microscopic examination is finished.

Restoration of the Body.—The cavities opened are wiped dry. Openings in the neck likely to drain into the mouth, and defects in the pelvic floor, had best be closed preferably by suture and by packing with gauze or, what is still better, gauze pads containing bran. Such pads may also be used for re-establishing the contour of the body, preventing collapse of the sternum, and, if the larynx and trachea have been removed, may be used for restoring the rotundity of the neck. The breast-plate is replaced and loosely attached in position by lateral sutures. The incision in the anterior median line is now closed. If just before the last stitches are tightened 300 or 400 c.c. of formalin is poured into the body cavity, its absorption by the bran will greatly retard decomposition.

The Head.—The brain should rarely be returned to the skull cavity, as it rapidly softens and forms a semifluid material that tends to escape in spite of the usual precautions. The cranial cavity may be loosely

packed with paper, cotton, or bran pads, or oakum, which I believe is the best. Many ingenious methods have been devised for retaining the calvaria in position. If the temporal angles are broken out with a chisel, usually there is enough beveling to prevent lateral displacement. This is particularly true if the temporal fascia and muscle above and below the line of incision are sutured tightly. Where a circumferential cut has been made, it is best to fasten the skull cap in position by wire sutures introduced through drill-holes in the temporal and occipital regions. Where the ordinary V-cut recommended on page 21 is employed, Slee's ingenious method will be found useful. The anterior saw-cut is extended 1 or 2 cm. backward in each temporal region; the posterior cut is projected forward in a like manner. Through these two slits narrow roller bandages are passed, the calvaria replaced, and the bandages carried upward, drawn tightly over the convexity, and pinned in two places. The skin flaps are then replaced and sutured. The spinal canal is wiped dry, loosely packed with cotton, sawdust, bran, or candle-wicking, the bone replaced, and the skin sutured in position.

Preservation of Tissues.—The substance commonly used for the preservation of specimens has been alcohol; with this reagent color is lost, density altered, and contour indifferently retained. Of late formalin[1] has been adopted as a routine preserving agent, the strength commonly used being ten parts of the commercial article and ninety parts of water. Specimens preserved in formalin may be carried into Müller's fluid for examination of the nervous tissues and may also be treated by Marchi's method for the demonstration of fat. They are better adapted to histologic examination than specimens preserved in alcohol, but for cytologic study compare unfavorably with specimens fixed by approved agents to be mentioned under Histologic Technic. For the brain, spinal cord, and peripheral nerves Orth's fluid is generally used. Müller's fluid is prepared as follows:

Potassium bichromate,	2.5 gm.
Sodium sulphate,	1.0 gm.
Water,	100.0 c.c.

Orth's fluid is prepared by adding—just before using—10 c.c. of formalin to 100 c.c. of Müller's fluid. The solution must be changed at the end of twenty-four to forty-eight hours, and by the third of fourth day had best be replaced by Müller's fluid. Large masses, such as the brain, require a longer time and should be freely incised when the solution is first changed. Orth's fluid, like that recommended by Müller, darkens the tissue, alters its macroscopic appearance, and is ill-adapted to material intended for gross demonstration or museum exhibition.

Organs or specimens not too large (one kilo) can be preserved in formalin vapor by placing them on a bed of cotton in an air-tight jar, previously moistening the cotton with pure formalin, and, for the first few days, keeping the specimen covered by filter-paper moistened with formalin.

For the preservation of color no method yields results comparable

[1] Formalin is a proprietary article—a forty per cent. aqueous solution of formaldehyde gas. The original formalin was expensive, but equally efficient solutions, under other names—as formalose, formol—can be obtained now at a price making preservation by this method cheaper than with alcohol.

to those obtained by that devised by Kaiserling, of which many modifications have been suggested.[1] Two solutions are necessary:

Solution A.		*Solution B.*	
Formalin, ...	250 c.c.	Acetate of potassium,	200 gm.
Nitrate of potassium, .	10 gm.	Glycerin, ...	400 c.c.
Acetate of potassium,	30 gm.	Water, ...	2000 c.c.
Water	1 liter.	Thymol to saturation.	

The specimen to be preserved is quickly and lightly washed in water to remove adhering blood only; it is then placed for from one to twenty-four hours in solution A, at the end of which time it is changed to fresh solution A, where it is allowed to remain for from two to thirty-six hours. Wash in running water for from fifteen minutes to one hour and transfer to eighty per cent. alcohol; as soon as the color begins to reappear the specimen is transferred to ninety-five per cent. alcohol, in which it should be allowed to remain until the color is fully restored. This process of development in the alcohol must be watched closely, for if allowed to go too far the color will be irretrievably lost; as soon as the color is restored transfer the specimen to solution B, which, at the end of twenty-four to forty-eight hours, had best be changed, as any residual alcohol tends to bleach the colors. In order to prevent the growth of molds solution B must be kept saturated with thymol, a small lump of which should be left constantly in all vessels containing the fluid. The same result can be accomplished by adding formalin, 0.75 to 1 per cent.

Specimens prepared by the Kaiserling method may be preserved without fluid in air-tight jars containing a lump of thymol. Littlejohn recommends this method for the preservation of stomachs from cases of corrosive sublimate, carbolic acid, and creosote poisoning, which may be kept indefinitely in air-tight jars, bacterial growth being prevented by the poison contained in the specimen.

Small cysts, such as those of the echinococcus, are best preserved in a ten per cent. aqueous solution of chloral.

[1] See papers by Coplin and also Herring ("Jour. Amer. Med. Assoc.," August 13, 1904); Watters ("N. Y. Med. Jour.," August 23, 1902); paper by M. E. Abbott ("Amer. Med.," April 4, 1903) on the "Classification of Museum Specimens"; also the writer's papers in the "Proceed. of the Path. Soc. of Philadelphia," 1903–1904 and 1904–1905. For the "Dangers of Formol" see Spitzka ("Science," July 17, 1903, p. 87).

CHAPTER II

HISTOLOGIC METHODS.[1]

Fixation.—Sections of the fresh tissue may be cut either free-hand or by means of Valentine's knife, which consists of two parallel blades of the utmost sharpness, separated from each other by a small aperture just as wide as the section is to be thick. Both methods are unsatisfactory, and are rarely used. Fresh tissue may be cut by freezing, as will be directed later, but for a satisfactory study of cell chemistry and morphology, and tissue architecture, it is especially important to subject the material to the action of some agent which will destroy all vitality, arrest metabolic and lytic processes, and prevent, as nearly as possible, all those postmortem changes which lead to chemic and structural alteration. This process is called *fixation* and the agents used *fixatives*. The following are especially commended:

(*a*) Chromo-aceto-osmic acid mixture (Flemming's solution). For this solution keep on hand the following stock solutions, and make up for use as wanted, in the proportion given:

Stock solutions to be kept on hand.	*Quantity needed to make up Flemming's solution.*
1 per cent. aqueous solution of chromic acid, ...	25 volumes.
1 " " " " osmic "	10 "
1 " " " " acetic "	10 "
Water, ...	55 "

All the water used in making the stock solutions or the final mixture must be distilled, and all containers should be chemically clean and dust-free.

Fixation of small pieces will be complete in from one-half to two hours, although a longer time may do no injury. A period beyond a few hours, however, is likely to make the tissues brittle After fixation, wash thoroughly in water. This is best accomplished by washing in flowing water for at least six hours. Proceed to embed at once or preserve in seventy per cent. alcohol until needed.

(*b*) Platino-aceto-osmic mixture (Hermann). Like the foregoing, it is best freshly prepared:

Stock solutions to be be kept on hand.	*Quantity needed to make up above solution.*
1 per cent. aqueous solution of platinic chlorid, ...	15 volumes.
2 " " " " osmic acid, ...	2 "
Glacial acetic acid, ...	1 volume.

[1] In the present edition of this book there have been inserted, whenever their importance seemed to demand it, such technical directions as may be necessary for the demonstration of special reactions or methods. When searching for directions bearing on some point, the student is advised to consult the index. No attempt can be made in such a work as this to go into the subject of histologic technic with elaborate detail. A few methods can be taught, it is believed, thoroughly; but for further detail as to special methods the student had best familiarize himself with that best of all books for the worker with the microscope, "The Microtomist's Vade-mecum," by Arthur Bolles Lee. See also references on p. 1.

This solution is used as already directed for Flemming's solution, and should be followed by the same careful washing. Tissue so prepared may be treated as already directed for tissue prepared in Flemming's solution.

(*c*) The most useful fixing agent for general use is corrosive sublimate. In solution it keeps well and fixes thoroughly, although for pure cell study the foregoing solutions are probably better. Heidenhain's solution is prepared by dissolving 125 gm. of corrosive sublimate in a liter of 0.5 per cent. solution of sodium chlorid in water. The solution of the corrosive sublimate being effected in the boiling salt solution, on cooling its crystals are thrown down, but are again taken up as the solution is used over. Small pieces of tissue fix in this solution in from one-half to two hours. The used solution is filtered back into the stock solution, and the tissue washed in water or, what is better, seventy per cent. alcohol. A little experience soon enables one to infer when the stock solution has become exhausted. The fixing solutions of Zenker, Petrunkevitch, and Bensley are also excellent for routine work.

Petrunkevitch's Solution.

Alcohol, absolute, ...	200 c.c.
Water, ...	300 c.c.
Glacial acetic acid, ...	90 c.c.
Nitric acid, pure conc.,	10 c.c.
Corrosive sublimate, ..	55 gm.

Bensley's Solution.

Potassium bichromate, 1 % aqueous solution, ...	50 c.c.
Corrosive sublimate, saturated alcoholic solution, ...	50 c.c.
Glacial acetic acid, ...	5 c.c.

The solutions must be kept separately and mixed when needed.

The tissues are transferred from this solution to seventy per cent. alcohol containing a trace of iodin; this should be changed frequently and the specimens kept in seventy per cent. alcohol until needed. Zenker's, Bensley's, and Orth's fluids require from twelve to twenty-four hours for fixation; the tissues should then be washed in running water and finally carried through iodized alcohol. Tissues fixed in mercurial solutions contain crystals which must be removed, as they obscure the microscopic picture, and, I am inclined to believe, corrosive sublimate left in a specimen renders it more dense, and with hard structures such as fibrous tissue and masses of unstriped muscle (uterus), the intense hardening may prevent satisfactory sectioning. The corrosive sublimate may be removed after sectioning (p. 41) or during the process of dehydration; if the seventy, eighty, and ninety per cent. alcohols are faintly tinged (light canary yellow) by the addition of iodin, the sections will contain no mercurial precipitate; the iodin must be thoroughly removed in subsequent alcohols, otherwise the tissues will be brittle.

In fixing by any of the above methods, the tissue should be in small pieces, not larger than 0.5 to 1 cm. cube. The quantity of the fluid used should be abundant, and exceed several times the volume of the tissue to be fixed.

For the preparation of tissue containing nerves, or the central nervous system, nothing has been more generally used than bichromate of potassium. It is used in two to five per cent. aqueous solutions, or as Müller's or Orth's fluids (p. 31); it also enters into Zen-

ker's and Erlicki's solution, the former much, and the latter but little used.

Zenker's Solution.

Corrosive sublimate,	2.5 gm.
Müller's fluid,......	100.0 c.c.
Just before using add	
Glacial acetic acid	5.0 c.c.

Erlicki's Solution.

Potassium bichromate,.........	2 gm.
Copper sulphate,...	1.08 gm.
Water,...........	100.0 c.c.

Orth's and Erlicki's fluids fix and harden much more rapidly than Müller's fluid alone; in either of these solutions a spinal cord would require but two or three weeks, or even less, while with Müller's fluid a much longer time is necessary.

Alcohol is sometimes used as a fixative. To be efficient it must be as nearly absolute as possible. Weaker solutions give rise to easily recognized and quite characteristic artifacts. When rapid fixation and coincident dehydration are desirable, a saturated alcoholic solution of corrosive sublimate may be used. For the demonstration of bacteria in tissue, fixation by alcohol is permissible; it has, however, no advantages over corrosive sublimate, even for this purpose, and is always associated with a very grave disadvantage, in that one desiring to study the nuclei may find that the fixative has not properly preserved them.

Alcohol is largely used as a dehydrating agent and for the preservation of tissues during the interval between fixation and the final steps in the embedding process. It is the ideal agent for neither purpose, but for the present it seems to be the best that we possess.

SECTION CUTTING.

Infiltration Methods.

1. Paraffin.—After fixing and washing as already directed, the tissue to be infiltrated is dehydrated by passing through alcohols of increasing strength — seventy per cent., twenty-four hours; eighty per cent., twenty-four hours; ninety per cent., twenty-four hours; absolute, twenty-four hours. As alcohol does not mix with paraffin, it must be displaced by some paraffin solvent. For this purpose numerous reagents have been used, such as chloroform, turpentine, xylol, toluol, benzol, cedar oil, and many allied bodies. Many of these alter the tissues; probably all of them do slightly, but the least objectionable is cedar oil. From absolute alcohol the tissue is carried into the clearing agent, preferably cedar oil, and, to make the change gradual, the cedar oil is diluted with an equal part of absolute alcohol; after twenty-four hours' treatment in this mixture the tissue is transferred to pure cedar oil for

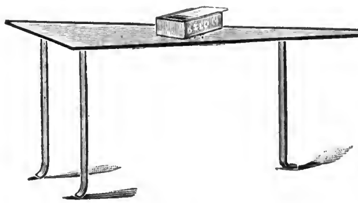

FIG. 30.

Flat-iron-shaped copper table, which may be used for paraffin infiltration as well as for the fixation of blood films. If a Bunsen burner be placed under the tip of the sharpest corner, to the right of the single leg, and the strip be heated to a constant temperature, so that the extreme end from the burner may be cold any degree of temperature between the cooler part and that part over the burner, which is practically red-hot, may be obtained. As shown in the cut, a small paraffin dish is placed over a spot where the paraffin is kept barely melted.

twenty-four hours, and then to cedar oil containing sufficient paraffin to thicken it perceptibly; twenty-four hours later the specimen is placed in melted paraffin, the melting-point of which should be 50° C. in summer and 45° C. in winter. The paraffin must be kept as near the melting-point as possible by means of a paraffin oven and a thermoregulator. After from six to twenty-four hours the tissue is transferred to fresh

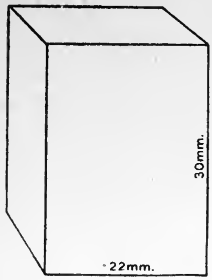

FIG. 31.
Block of hard wood or of rubber fiber as usually received in the laboratory.

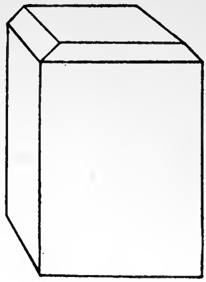

FIG. 32.
Same block as figure 31, with corners properly trimmed to receive paraffin or celloidin for embedding.

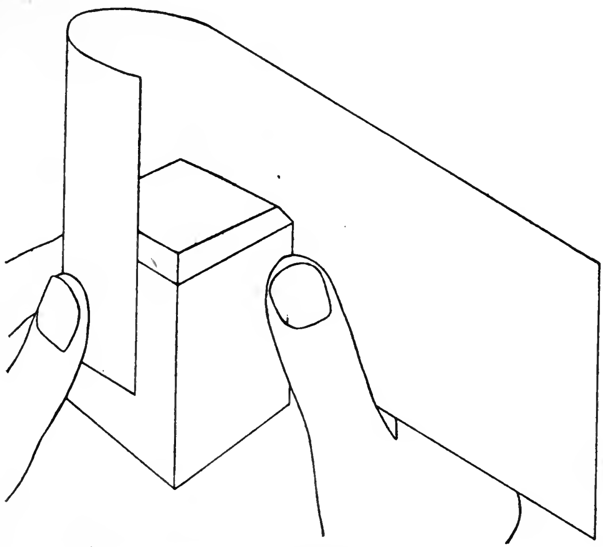

FIG. 33.
Method of applying paper to block.

paraffin at the same temperature, in which it is kept from twelve to twenty-four hours. The gentle heat, continuously applied, displaces the cedar oil and permits the paraffin to infiltrate the interstices of the tissues. One end of a wooden block—about a two-centimeter cube—is warmed over a Bunsen burner and dipped in the melted paraffin. It is then wrapped with a strip of paper four centimeters wide, so that the

paper projecting from the warmed and coated end of the block forms a well deeper than the tissue to be mounted. The block of tissue is then placed in position at the bottom of the well, arranged to cut to the best advantage, and melted paraffin poured in until the well is filled. This is allowed to cool and the paper is then removed. The paraffin is now gray, appears granular, and is said to be in the crystalline form; if put in a warm place,—care being taken that it is not warm enough to melt the paraffin,—it soon becomes transparent, or, it is said, the paraffin becomes amorphous, homogeneous, or hyaline.

The block is now ready to cut. It is trimmed down nearly to the tissue, each side being cut so as to present a surface square to the knife, the general aspect of the block being that of a truncated pyramid. The paraffin trimmed off is remelted, and may be used many times. The block is clamped in the holder of the microtome so that the cutting-edge of the knife strikes squarely against the block along its whole length,

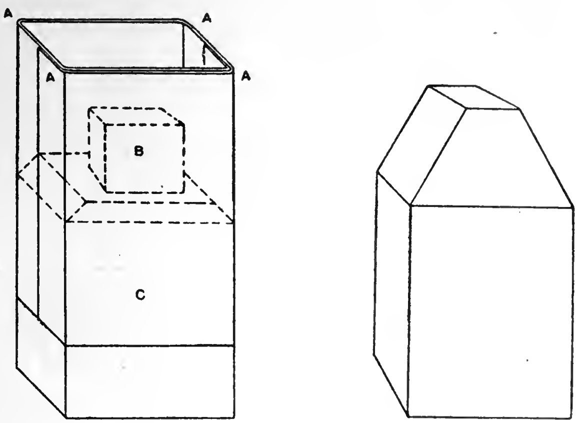

FIG. 34. FIG. 35.

Paper (A, A, A, A) properly wrapped around block (C), with block of tissue (B) to be embedded, ready for pouring the paraffin in and completing the cast. After the cast cools (see text) the paper is removed and the paraffin is trimmed, as shown in figure 35, carefully avoiding the block of tissue, which should be thoroughly covered by the paraffin at all points.

the knife is so arranged that it cuts like a chisel, and not with a drawing motion. To get the best sections, the paraffin must be of the proper temperature, as this determines the density; in summer the block may have to be cooled by ice; in winter it may require warming.

The most important factor in paraffin infiltration is thorough dehydration and clearing. Absolute or approximately absolute dehydration is necessary in order to secure penetration of the clearing agent—cedar oil, xylol, or whatever it may be. If the pieces of tissue are small, the stages of the process may be shortened. Tissue kept too long in strong alcohol or in the clearing agent or paraffin (warm) not infrequently becomes brittle. The occurrence of this condition should lead the worker to shorten the stages sufficiently to overcome the difficulty. When osmic acid methods have been used for the purpose of determining the presence of fat, the clearing agent and paraffin may, under some

conditions, partly remove the fat. In osmic acid preparations, when the fat is to be retained, celloidin infiltration is to be preferred.

It will be seen that the foregoing process requires days, and to overcome this objection Reeves has recommended the following: (1) Fix in saturated alcoholic solution of corrosive sublimate for one hour.

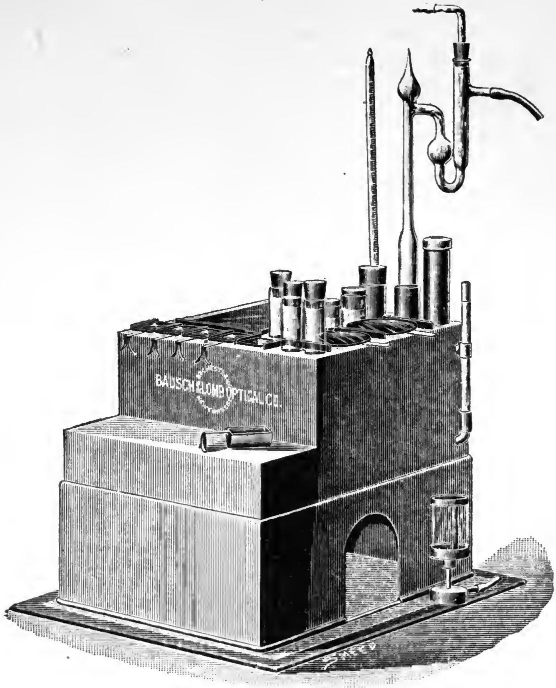

FIG 36.—NAPLE'S PARAFFIN BATH FOR INFILTRATING TISSUES IN PARAFFIN.
The apparatus consists essentially of a series of receptacles for holding the melted paraffin, with a surrounding water-bath retained at an even temperature by a thermoregulator.

By this method fixation and dehydration go on together; (2) absolute alcohol, one hour; (3) xylol, one hour. As xylol has a very low volatilizing point, it quickly evaporates in the paraffin bath, and permits the rapid penetration of the paraffin; it is kept one hour in the first

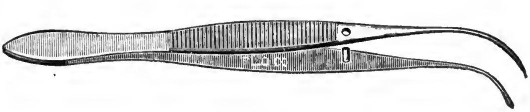

FIG. 37.—FORCEPS CONVENIENT FOR HANDLING COVER-GLASSES, BLOCKS OF TISSUES AND SECTIONS.

paraffin and one hour in the second, when it is cast. In order to prevent crystallization of the paraffin the cast is plunged into ice-water as soon as its surface has cooled sufficiently to form a thin film; the cooling may be facilitated by holding the block out of the window in winter or by gently blowing upon it in summer. The cast is now

trimmed and cut. Of course, the pieces of tissue to be prepared in this way must be very small,—not over 0.5 cm. cube,—and the results can not be considered as comparable to the slower method already described.

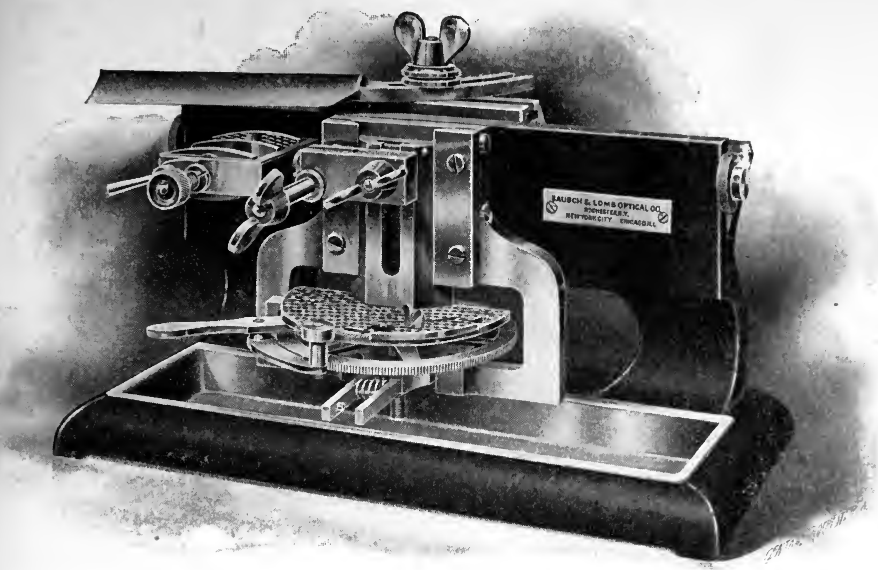

FIG. 38—LABORATORY MICROTOME.

Can be used, as shown in the cut, for celloidin sections; an attachment for freezing may be substituted for the clamp shown in the illustration immediately below the knife. For paraffin blocks the knife must be turned with its cutting-edge at a right angle to the plane of the knife-carrier.

Mounting Paraffin Sections.—If the sections be properly cut and the infiltration has been satisfactory, they will adhere in chains or ribbons as they come away, or each section may be removed from the knife as rapidly as cut, using a short sable brush for the purpose. To insure thin sections, the knife must be of the utmost sharpness. Be-

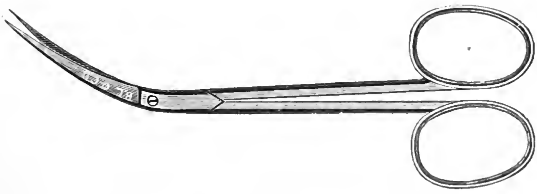

FIG. 39.—SMALL MICROSCOPIC SCISSORS.

Suitable for trimming sections and labels and for other microscopic work.

fore the sections are cut it is best to prepare the slips to receive them. The slips or slides are thoroughly cleansed with alcohol and dried, using toilet-paper or a soft cloth for that purpose. Place on the center of the slide a very small quantity—less than a drop—of Mayer's

albumin, and with a perfectly clean finger wipe it off. This leaves an almost imperceptible layer of the albumin. On this place a few drops of water,—enough to float the section just clear of the albumin,

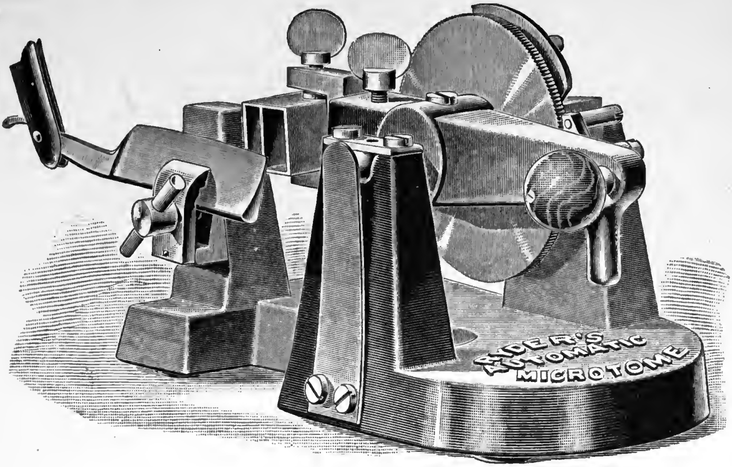

FIG. 40.—RYDER MICROTOME.
Expressly adapted for paraffin sections and for cutting in series; can not be used for frozensections. May be employed for celloidin if the chloroform method ot hardening has been adopted.

—and place the section on the water; gently warm the slide, being careful not to melt the paraffin; as the section becomes warm it will straighten out, all folds and wrinkles disappearing. Now carefully pour off the excess of water, and the section falls upon the layer of albumin,

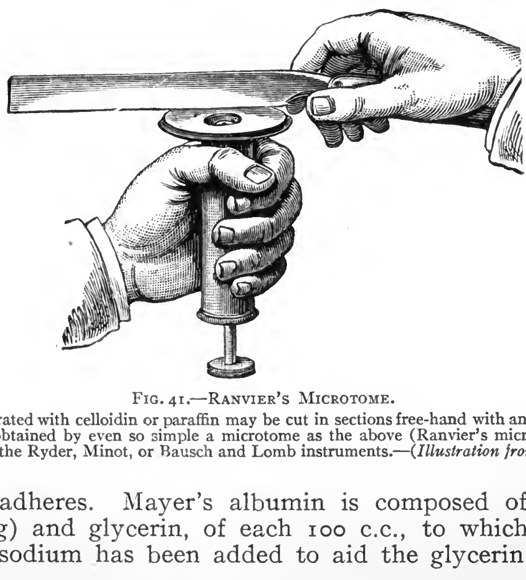

FIG. 41.—RANVIER'S MICROTOME.
Blocks of tissue infiltrated with celloidin or paraffin may be cut in sections free-hand with an ordinary razor; better results may be obtained by even so simple a microtome as the above (Ranvier's microtome) or very much better results by the Ryder, Minot, or Bausch and Lomb instruments.—(*Illustration from Gould's Dictionary.*)

to which it adheres. Mayer's albumin is composed of egg-albumen (white of egg) and glycerin, of each 100 c.c., to which one gram of salicylate of sodium has been added to aid the glycerin in preserving

the albumin; after thoroughly mixing, the mass is filtered through paper—a process requiring weeks. The albumin fixes the section to the slide, so that it may be taken through the subsequent processes without danger of becoming detached. After the section has been drained of the water upon which it was floated to facilitate flattening, it is placed in a drying oven to get rid of any remaining water In ordinary work where no great haste is demanded the slide may be placed in some warm place, protected from the dust, until perfectly dry. After drying, which may require from four to twenty-four hours, the slide is gently warmed until the paraffin just melts, and no more; it is then thrust into ordinary kerosene, or, what is slightly better but much

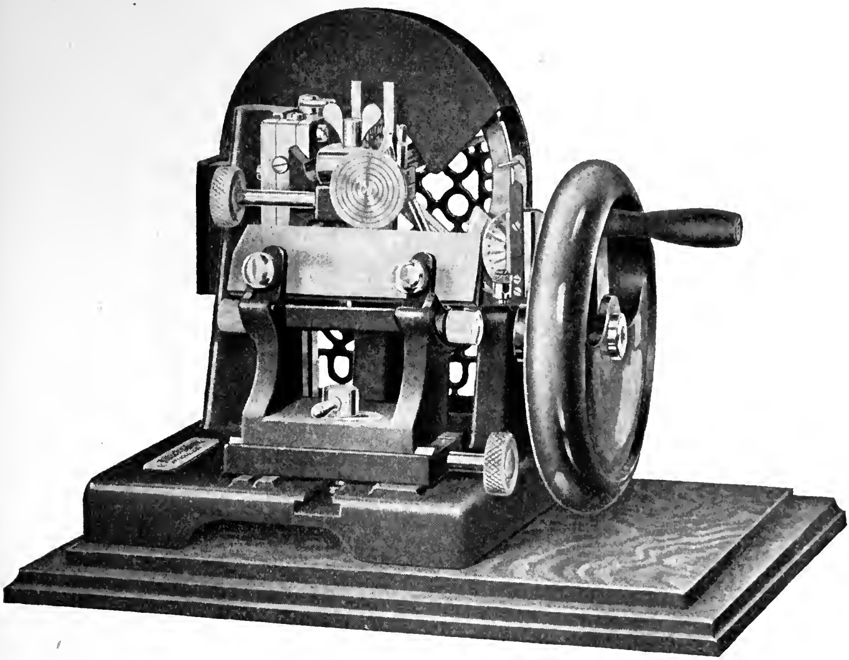

FIG. 42.—MINOT MICROTOME.

Two sizes of the instrument are made: the illustration is of the smaller size. The corrugated metal plate just above the knife is intended to receive the block of tissue which is cemented on by the use of melted paraffin. The writer has found this extremely difficult and tedious, and has devised a clamp which replaces the complicated orienting attachments shown in the cut, and grasps the block shown in figure 35, without the necessity of cementing the tissue to the microtome.

more expensive, xylol; either of these quickly removes the paraffin, usually requiring about fifteen minutes; wipe off the excess of xylol, rinse the mount in alcohol, and place the slide in that liquid until the xylol is removed. From the alcohol the section is stained as will be directed later. If the tissue was fixed in a solution containing mercury this must be removed by treating the section with tincture of iodin, in which it is immersed for fifteen minutes; it is then washed with a few drops of alcohol and placed in a jar of alcohol, from which it is removed for staining when desired. If the block of tissue was

carried through iodized alcohol, the section need not be treated with the tincture.

2. **Celloidin Infiltration.**—Celloidin is a proprietary product first used in photography, and is nothing more than a nonexplosive gun-cotton. As used, it is dissolved in equal parts of alcohol and ether, thus making a collodion that, so far as the author can observe, has no advantage over a good collodion made from gun-cotton. The alcohol used for this purpose should be absolute; the solution will be facilitated by placing the celloidin in a tightly stoppered bottle—a citrate of magnesia bottle is to be recommended—and pouring on the absolute alcohol, which should be allowed to remain in contact with the celloidin for twenty-four hours, when an equal volume of ether should be added. By this method

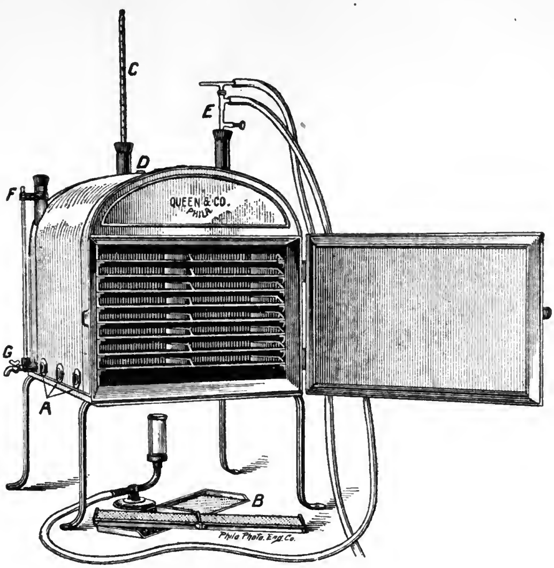

Fig. 43.—Drying Oven.

A. Three tubes for admitting air to interior. At *D* are three similar exit tubes. *B*. Shelves upon which slides are placed at the student's desk, from which, after labeling each slide and placing under the slides a piece of paper with his name and desk number, he places the tray in the oven. *C*. Thermometer. *E*. Thermoregulator. *F*. Water-gage. *G*. Cock for emptying the water space. The temperature of the oven should never reach the melting-point of the paraffin, and had best be between 37° C. and 40° C.

solution will be complete and no time will be lost. As ordinarily used, two solutions are needed—one a thick, syrupy solution, and a second thin solution made by diluting the thick solution with an equal quantity of absolute alcohol and ether. The tissue to be infiltrated is fixed and dehydrated as already described for paraffin; it is then placed for twenty-four hours in a mixture of equal parts of alcohol and ether. From this the tissue is transferred to the thin solution of celloidin. The best results are obtained by leaving the mass for infiltration several days in this solution, when it is placed for an equal length of time in the thick solution. A block is then soaked in alcohol and ether for one or two hours or longer, and one end is coated with celloidin and wrapped in paper, as already directed for paraffin. Into the well the infiltrated

piece of tissue is placed, arranged as desired for cutting, and the thick celloidin solution is poured over it; the mass, which is now said to be cast, is placed under a lightly fitting bell-jar or cover until the celloidin begins to set, when it is thrown into eighty per cent. alcohol for hardening. At the end of twenty-four hours it will be found sufficiently hard for cutting, but it may be kept indefinitely in the alcohol and cut when desired. Unlike paraffin, celloidin must be cut with the microtome knife at an angle to the block,—that is, with a drawing motion,—and, while the paraffin was cut with a perfectly dry knife, the celloidin must be cut with a knife kept flooded with eighty per cent. alcohol. Each section is removed from the knife as cut and is transferred to eighty per cent. alcohol, in which it may be preserved until wanted for use. The great advantage claimed for celloidin is that, unlike paraffin, it need not be dissolved out before the section is stained. Stains such as carmin and hematoxylin may be used, the celloidin holding the sections together during the manipulations incident to staining.

Gilson's Method.—A satisfactory method of celloidin infiltration is that devised by Gilson, in which, after dehydration and treating with the alcohol and ether mixture, the tissue is placed in a test-tube con-

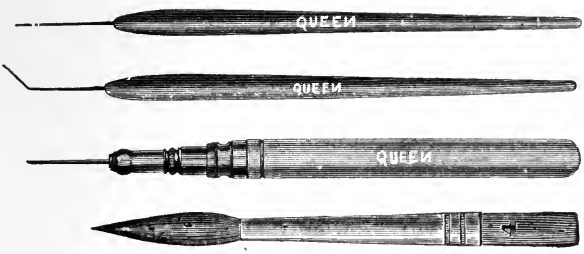

Fig. 44.—Needles and Brush Suitable for Handling Sections.

taining several cubic centimeters of thin celloidin solution; after a few days in the thin celloidin, the test-tube is immersed in a water- or paraffin bath at about 42° C., at which temperature the solvents (alcohol and ether) rapidly evaporate, thereby hastening penetration and increasing the density of the infiltrating mass. When the solution has evaporated to about one-third its original bulk, it is turned out and cast as in the slow process. The hardening of the block is greatly facilitated and the results are improved by hardening in chloroform. The chloroform hardening process is applicable to blocks that have been infiltrated either by the slow or by the rapid method.

As soon as possible after the cast is made the mass is placed in a desiccator or sieve dish, or in a bottle containing a teaspoonful of chloroform and having a tightly fitting stopper. A support is arranged above the chloroform, on which the block to be hardened is placed, and the vessel is then tightly closed. From two to twelve hours will be sufficient for the hardening, after which the block is placed in a mixture of cedar oil two parts and chloroform one part; more cedar oil is added from time to time until nearly pure cedar oil is attained. The sections are cut dry, as in the paraffin method. The block may be preserved in-

definitely in the cedar oil.[1] After cutting, the sections are washed in alcohol in order to remove the cedar oil, and may then be stained.

Sections obtained by the celloidin embedding and infiltration process may be secured to the slide by ether vapor or by a very thin layer of celloidin. The best method is to float the section on to the slide, blotting it carefully with bibulous paper, and, from a bottle containing a small quantity of ether, to pour the vapor upon the section. This will sufficiently soften the celloidin to make it adhere to the slide during the subsequent manipulation. It is to be remembered that celloidin sections must be kept moist throughout the entire course of their preparation. Drying them is, as a rule, injurious, if not destructive.

3. **Congelation Method.**—Fresh tissue may be frozen and sectioned, but the best method is that of Hamilton: (1) Harden; (2) wash out the hardening fluid; (3) place in sugar solution for from two to twenty-four hours; this solution is composed of two ounces of sugar dissolved in one fluidounce of water; after removing from the syrup, wash lightly in water and (4) place in mucilage for two hours. The tissue may now be put on the drum of the freezing microtome, frozen, and cut. Remove sections from the knife with a soft brush, and wash them thoroughly in water to remove the gum and sugar; the staining is proceeded with as for other sections.

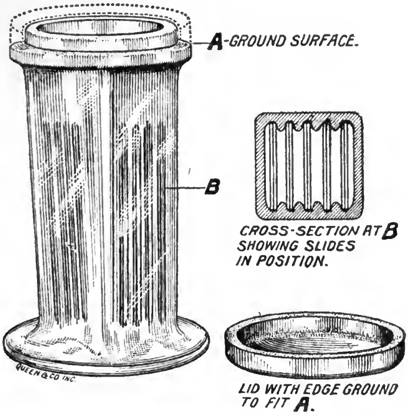

FIG. 45.—DISH FOR REMOVING PARAFFIN AND CORROSIVE SUBLIMATE AND FOR DEHYDRATING.

May also be used for staining, and for the same purposes as the Stender dish. After the sections are cemented on the slide the slides are placed back to back and slipped down in the groove, as shown at B at the bottom of the dish. If the slides are thin, the dish will hold ten at one time.

Remarks on the Foregoing Processes.—For small pieces of tissue the paraffin method is best; thinner sections can be cut, and the method of cementing them on the slide makes the handling most convenient. It is commonly stated that large blocks can not be sectioned by the paraffin method; this is true in part only. A specimen 0.5 cm. in thickness and 2 cm. square may be infiltrated thoroughly, and, under favorable conditions, with a good modern microtome, should yield sections not over 5 μ thick, and in skilled hands they may be cut even thinner. For large specimens, such as an eye, and for tissues from the brain, spinal cord, or larger nerve-trunks, celloidin is to be preferred. After using the freezing method to a very large extent for about ten years, the author is thoroughly convinced that it is not to be relied upon. The ice crystals that

[1] Since the publication of the last edition of this manual the writer has known of considerable difficulty due to softening of the celloidin when preserved in cedar oil. The cause of this unfortunate complication was not at first discovered. It would appear that the success of the method depends upon the quality of the cedar oil. Mayer has recently informed Harris that cedar oil prepared by Schimmel did not in the least affect the celloidin.

form in freshly frozen tissue break up the cells and give results that may mislead the most experienced investigator. The distortion of structure incident to the use of congelation masses, their macerating properties, and the difficulty in removing the infiltrate, have led me to give them up entirely for laboratory work; only the crudest kind of pathologic work can be performed by the freezing and congelation methods at present at our disposal, and the results are always open to criticism.

STAINING AND MOUNTING.

General Remarks.—As a rule, it is best for the student to work with one stain until he is familiar with it; and before combining two or more stains it is best for him to familiarize himself with the action of each stain when used alone. The student thould remember that there are two principles involved in staining: (1) When a stain shows unusual selectivity in certain bodies, such as cell nuclei, it is allowed to act long enough to color the desired bodies only; its action is then stopped and the preparation of the mount continued. (2) The stain is permitted to act until everything that will receive the color is stained, and then some agent is applied that differentiates certain elements by removing the stain from other structures. Thus, acid alcohol is used to differentiate in carmin staining, and water after hematoxylin. Alcohol or water, either of which may be used with or without acidulation, are also used to differentiate with the anilin dyes. The objection to examining sections unstained is that no one structure is prominent; and if everything in the section be uniformly colored, nothing is gained by the staining. For this reason differentiation is more or less applicable to all stains. After differentiation, or in some instances simultaneously with this process, dehydration is necessary in order to proceed with the next step—clearing the section. The process of clearing is necessary in order to examine the section by transmitted light. Clearing also makes the application of a permanent medium, such as xylol balsam, possible.

The clearing agents mentioned in the preceding and following pages are not all applicable under all circumstances. The best clearing fluids are xylol, cedar oil, creasote, and possibly one or two other agents having more or less special uses.

Carmin and Hematoxylin.—The two stains most frequently used in laboratory work are carmin and hematoxylin. Strongly alkaline stains, such as lithium carmin, are no longer to be commended; the same is true of bulk staining. The *carmin* most useful in the laboratory is Grenacher's alcoholic borax-carmin:

Alcoholic Borax-carmin.

Carmin (best No. 40),	3 parts.
Borax,	4 "

Mix thoroughly, pulverize in a mortar, and add 100 parts of water; boil for half an hour; add an equal bulk of seventy per cent. alcohol; set aside for one week, and then filter.

To stain, add enough of the stain to the section on the slide abundantly to cover it, and allow it to act for from five to ten minutes or

longer. Drain off the excess of stain, wipe around the section with paper or soft cloth, and apply acid alcohol.

Acid Alcohol.

Hydrochloric acid,	1 part.
Water,	29 parts.
Alcohol,	70 "

The section, as soon as the acid alcohol is applied, turns from a purplish-red to a light crimson, and becomes more nearly transparent; it is then washed in strong alcohol, the excess wiped from around the section, and the latter is covered with creasote. The alcohol dehydrates and removes the acid, which is the differentiating agent, and the creasote renders the section clear for examination by transmitted light. As soon as the section is clear remove the excess of creasote, apply a drop of balsam, and cover with a thoroughly cleansed cover-glass; label the section. It will now keep indefinitely.

Fig. 46.—Dropping-bottle with Barnes's Dropper, Which Closes the Mouth of the Bottle Like a Rubber Stopper. These bottles are usually of one ounce capacity, and are convenient for holding stains and staining reagents.

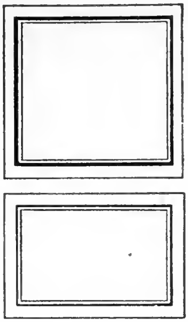

Fig. 47.—Proper Size Labels for Labeling Microscopic Slides.

One of the best carmin stains is *Mayer's carmalum.* This is made by dissolving 1 gm. of carminic acid and 10 gm. of alum in 200 c.c. of distilled water, using heat if necessary. In order to preserve the solution add 0.1 per cent. of salicylic acid, or 0.5 per cent. of salicylate of sodium. The solution is clarified by decanting or, better, by filtration. The great advantage of this solution lies in the fact that it is almost impossible to overstain with it, and by careful washing and differentiation practically all intermediate degrees of staining can be obtained. It may be differentiated in acid alcohol, as already directed for borax-carmin, or, if the alcohol used for the subsequent dehydration be strongly tinted by the addition of picric acid, the combined action of the two stains (the carmin being a nuclear stain and the picric acid a protoplasmic stain) will afford one of the best general stains found in the laboratory. Picric acid may be used in the same way with borax-carmin, but the result is not so satisfactory.

Hematoxylin Staining.—The classic form of this stain is Delafield's, made as follows: Dissolve 4 gm. of hematoxylin crystals in 25 c.c. of strong alcohol; add this solution to 400 c.c. of a cold, filtered, saturated aqueous solution of ammonia alum; expose to light and air for several days. Filter, and add glycerin 100 c.c. and methyl alcohol 100 c.c.

Allowed to stand in the light, with the bottle loosely corked, this mixture turns dark purple, almost black; it should then be filtered and kept in tightly stoppered bottles. For use it should be much diluted; the amount of dilution must be determined for each lot, varying with the

degree of oxidation and with the age of the stain. If made with distilled water, and provided that all vessels and containers are kept chemically clean, this stain will keep for years. The objection to this stain lies in the fact that it requires time for ripening, and hence cannot be made and used at once. Harris overcame this difficulty by artificially oxidizing the hematoxylin into hematein. *Harris's hematoxylin* is prepared by dissolving one gram of hematoxylin in 10 c.c. of alcohol and adding the resulting solution to 200 c.c. of distilled water in which 20 gm. of ammonia or potassium alum have previously been dissolved. The fluid is placed in a flask and rapidly heated to boiling, at which time 1 gm. of mercuric oxid is added. The solution at once darkens (ripens) and should be rapidly cooled in running water; the stain is now ready for use, but should be diluted. From this stock solution an *acid glychæmalum* may be prepared by adding 4 c.c. of glacial acetic acid and 30 c.c. of glycerin to 70 c.c. of the stock hematoxylin solution. This acid hematoxylin, strongly resembling Ehrlich's acid hematoxylin and Mayer's acid hemalum, has the great advantage that it is almost impossible to overstain with it.

To use the hematoxylin of Delafield or Harris the sections cemented on the side, as already directed, or in the case of celloidin loose sections, are covered with the diluted stain for from five to fifteen minutes, washed in water, dehydrated in alcohol, cleared with creasote, and mounted in balsam as directed in the last steps for carmin, except that differentiation is secured by the use of water, and not by acid alcohol. A better stain is secured by taking enough distilled water in a bottle or staining dish to immerse the slide on end; to this add sufficient hematoxylin to tinge the water rather deeply; the sections, cemented on the slide, are left in this overnight (or even for twenty-four hours), washed in water, and treated as previously directed. Hematoxylin not only stains the nucleus, but affords a light tint to the protoplasm as well. This latter, however, can be better secured by using eosin. After the section is stained in hematoxylin and washed in water, the excess of the water is removed and the section is treated for a moment in an alcoholic solution of *eosin* (0.5 per cent.) followed by alcohol and creasote, and is then mounted in balsam. The nuclei are stained purple by the hematoxylin and the cell protoplasm pinkish by the eosin. This makes a very fair contrast stain, and brings out some elements not shown by the hematoxylin. In addition, it shows red blood-corpuscles to advantage, being a specific stain for hemoglobin. *Picric acid* may be used with hematoxylin to advantage, particularly if the sections are a little thick or if they are overstained in the hematoxylin. After washing the hematoxylin stain thoroughly in distilled water, the subsequent dehydration is accomplished by the use of alcohol containing a trace of picric acid. The nuclear stains obtained by this method are sharp, and the yellowish protoplasmic tints are beautifully transparent.

For routine work I am unfamiliar with any contrast stain superior to that suggested by Van Gieson. Various strengths have been recommended, but the following, which may be further diluted with picric acid if necessary, will be found satisfactory:

Van Gieson's Solution.

Acid fuchsin, 1 per cent. aqueous solution,	15 c.c.
Picric acid, saturated aqueous solution,	50 c.c.
Water,	50 c.c.

Sections are stained deeply with hematoxylin, washed in water, treated with the above solution for from one to four or five minutes, rapidly dehydrated, cleared, preferably in xylol, and mounted in xylol balsam. The connective tissue is red or pinkish-red, the cell protoplasm of a yellowish tinge, and the nuclei a dark brownish or reddish-purple. In properly fixed preparations containing nerve-fibers the axis-cylinders stain red.

Anilin Dyes.—In addition to the use of these agents for staining bacteria, they have become important and useful adjuvants in certain microchemic reactions, which will be referred to under special headings throughout the book; and also for general stains. For practical purposes the anilin dyes may be divided into two groups:

1. Basic group, in which the staining property is due to the base present in the compound.

2. Acid group, in which the staining property is due to the acid principle.

The basic colors are, as a rule, sharp nuclear stains, while the acid dyes stain, more or less diffusely, the protoplasm in the cell. As a rule, the dyes are used as concentrated solutions (1) in water; (2) in five per cent. carbolized water; (3) in thirty to sixty per cent. alcohol, preferably about fifty per cent. Under some conditions the dyes seem to act best if the solutions are rendered faintly alkaline; or at other times, faintly acid. The alkalinity is usually secured by the addition of a very small quantity of carbonate of potassium, and the acidity by an extremely dilute solution of acetic, formic, or hydrochloric acid. The basic anilin dyes commonly used are safranin, fuchsin, methylene-blue, thionin, gentian-violet, toluidin-blue, etc. The acid stains mostly used are eosin, orange G, acid fuchsin, etc.

The following formulas and methods are introduced as examples, and after the student has familiarized himself with the technic given, he may apply the knowledge so obtained to staining with other and similar anilin dyes.[1]

Safranin is a most excellent nuclear stain. The following formulas are to be recommended:

Saturated solution of safranin in water, heated to 75° C.; after thorough saturation, filter; stain from two to five minutes to twenty-four hours, depending upon the tissue, length of fixation, etc.; wash in water, differentiate and dehydrate simultaneously in alcohol, clear in xylol, and mount in xylol balsam. A mixture composed of one part of the above solution of safranin and one part of a saturated alcoholic solution of alcohol-soluble safranin makes a satisfactory stain, and may be used in the same way.

Methyl-violet.—One or two per cent. solution in water. Stain from two to five minutes or longer, and treat in the same manner as already given for safranin.

Polychrome Methylene-Blue[2] (Unna) is a most acceptable stain for

[1] One of the great difficulties with anilin dyes is the inconstancy of their composition and the unreliability of many samples placed on sale. For this reason it is recommended that in purchasing the anilin dye the student should always specify the make of Grübler.

[2] This stain resembles, when diluted, Löffler's alkaline methylene-blue, the formula of which is as follows:

Saturated alcoholic solution of methylene-blue, ...	30 c.c.
Potassium hydrate (0.01 per cent. aqueous solution), ..	100 c.c.

May be used for staining tissues, but is more useful in bacteriologic work.

routine laboratory work. Although the formula for making this dye is easily accessible, satisfaction can best be obtained by purchasing the prepared stain from Grübler. One part of the dye to two or three parts of water is the best strength. Sections should be stained for fifteen minutes to several hours, washed in water, dehydrated, cleared in xylol, and mounted in balsam. The most beautiful results are obtained by glycerin-ether or styrone differentiation, both of which are described below. Contrasts with eosin may be obtained by staining in a 0.1 per cent. aqueous solution of water-soluble eosin; wash lightly with water and transfer to the polychrome blue; the latter tends to remove the eosin, and hence success depends on accurately judging the time necessary for immersion in the polychrome solution. Nothing but patient experimentation can accurately inform the beginner, but success repays him for the time and labor expended.

Toluidin-blue.—Dissolve one part of the dye in 100 parts of a five per cent. solution of carbolic acid in water; stain from five to ten minutes to twenty-four hours, differentiate and dehydrate in alcohol, clear with cedar oil, and mount in xylol balsam.

Ziehl's Carbolfuchsin.—Rub up 1 gm. of powdered basic fuchsin with 10 c.c. of alcohol in a glass mortar; dissolve 5 gm. of crystalline carbolic acid in 100 c.c. of distilled water; mix the two solutions and the stain is ready for use. The stain may be prepared by the addition of 10 c.c. of a saturated alcoholic solution of basic fuchsin to 90 c.c. of a five per cent. aqueous solution of carbolic acid. Stain sections two to five minutes to several hours; differentiate and dehydrate in alcohol, clear in clove oil or xylol, and mount in xylol balsam.

As a rule, sharpness of nuclear stain is obtained by overstaining, followed by careful *differentiation*, which must be stopped at a certain time; the best results are obtainable after repeated experiments and many failures. Alcohol as a differentiating agent does not give the best results, nor is the differentiation in alkaline or faintly acidulated water ideal. Two of the most satisfactory differentiating agents with which the writer is familiar are glycerin-ether and styrone.

The **glycerin-ether mixture** (Unna) is obtained from Grübler; the proper dilution is one part of the agent to fifteen of water. Sections are stained rather deeply in Unna's polychrome methylene-blue or in carbol-toluidin-blue, rinsed in water, and covered with the diluted glycerin-ether mixture. At first the dye comes out in clouds; later, differentiation progresses more slowly. The exact point at which to arrest the differentiation can be learned by experience only. In order to arrest the action of the glycerin-ether the excess is poured off, the section washed in water followed by rapid dehydration and clearing in xylol or cedar oil, and finally balsam. Many bacteria are beautifully stained by this method.

Styrone is a solid, camphor-like body at a low temperature; at the ordinary room-temperature it assumes a syrupy consistence. It is a differentiating fluid that also acts as a clearing agent and is superior to other differentiating agents in that the tissues may be watched under the microscope without a cover-glass, during the process of differentiation. In order to apply it, the section, stained as already advised for glycerin-ether, is hastily washed in water, followed by alcohol, and the styrone is at once applied. The styrone first applied becomes cloudy,

deeply dyed, and is poured off; fresh styrone is added, and the slide is placed on the stage of the microscope. As soon as the differentiation has become satisfactory the styrone is washed off with cedar oil, the application of the latter agent being continued until all differentiation has ceased; the cedar oil is then removed and xylol balsam and a cover-glass are applied. In clearing sections stained by basic anilin dyes disaster commonly follows the application of creasote. Xylol is considerably better, but the best results are obtained by the use of cedar oil, which acts slowly and must be given time; gentle warming hastens the clearing, but is rarely necessary if the dehydration has been complete.

Eosin may be used with either of the nuclear stains previously given. It is particularly useful with the toluidin-blue. Eosin, either as a saturated solution in water of the form soluble in that medium or saturated solution of eosin in alcohol, using the form soluble in that agent, may be used as contrast stains before or after the toluidin-blue or methylene-blue; as both of these agents are discharged by eosin solutions, it is possibly better to stain first with eosin, rinse in water, and apply the nuclear stain afterward. If the eosin be used after the nuclear stain, it should not be allowed to act too long, otherwise the nuclear stain may be discharged. As eosin acts as a differentiating agent, when used after the nuclear stain, care and experience are necessary to secure the best results. After the use of eosin, dehydration in alcohol and clearing in cedar oil are recommended.

For the use of eosin as a contrast stain with hematoxylin, see page 47. For the use of picric acid for the same purpose and with carmin, see page 46.

THE MICROSCOPE.

A Desirable Laboratory Microscope.—Figure 48 illustrates a stand useful in a pathologic laboratory. The horseshoe base gives solidity by its long arms and great weight. To this base is attached the upright, which supports the superstructure; the stand should be handled by this piece entirely, never grasping the parts above in moving the microscope, as such a procedure is likely to injure the adjustments. At the upper termination of the upright is the joint for inclining the microscope for convenience in working. Running to the front from this joint is the stage upon which the slide is placed for examination; clips are shown for retaining the slide in position. Beneath the stage are the substage mountings, consisting of diaphragms for lessening the light, condenser for increasing the rays' intensity, and a mirror for reflecting the light upward through the optic axis of the instrument. These parts are adjustable by lateral movement, by rack, pinion, and screw motion. Behind the inclination joint, and above the stage, what is known as the upright arm rises; at its upper part is placed the fine adjustment, worked by a milled thumb-screw. Passing off in front of this upright arm is the horizontal arm, to which is attached the coarse adjustment by rack and pinion moved by the milled heads shown at both sides. The tube carrying the optic parts is attached to the horizontal arm by the rack and pinion coarse adjustment. The tube is so made that it may be drawn out to a standard length. At the upper end of the tube is the eye-piece; at the lower end, the objec-

tive. In the laboratory instrument, when, for any reason, an oil-immersion objective may not be desired, two objectives (a $\frac{2}{3}$ of an inch and a $\frac{1}{4}$ or $\frac{1}{6}$ of an inch) are mounted on a double nose-piece, by means of which either objective may be brought into use. In bacteriologic examinations in which an oil-immersion lens is indispensable, three objectives are mounted on a triple nose-piece, as shown in the cut. (Fig. 48.) In nearly all cases the examination should *begin* with the lower power, followed, *if necessary*, by the higher power.

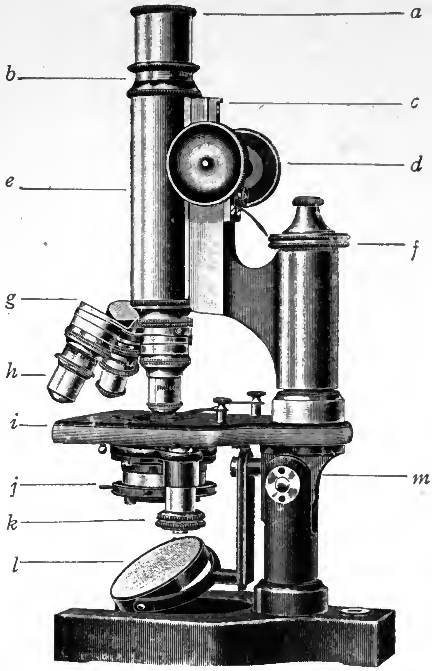

FIG. 48.—MICROSCOPE SUITABLE FOR GENERAL PATHOLOGIC AND BACTERIOLOGIC WORK.

a. Ocular or eye-piece. *b.* Draw-tube. *c.* Rack. *d.* Milled head of pinion moving the rack; the rack and pinion (*c* and *d*) together are called the coarse adjustment. *e.* Microscopic tube. *f.* Micrometer screw by which the fine adjustment is operated. *g.* Triple nose-piece or revolver which receives the objectives, *h;* in the above instrument there are three objectives which in turn may be rotated into the optical axis. *i.* Stage on the upper surface of which are clips for holding the slide during examination. *j.* Iris diaphragm in substage condenser; the diaphragm permits variation in the quantity of light admitted, and the condenser properly focuses the rays on the object examined. *k.* Screw for raising and lowering the condenser and by which the latter, when not in use, may be thrown to the side. *l.* Mirror for reflecting light into the optical axis of the instrument. *m.* Inclination joint permitting inclination of the instrument. The vertical column below the inclination joint is called the pillar and is solidly joined to the large, heavy horseshoe base supporting the instrument.

To Use the Microscope.—The instrument is placed in front and slightly to one side—usually the right side—of the observer; the student is advised to use the instrument with the stage horizontal, that is, without using the inclination joint. During the day, northern light or light from white clouds is preferable; if the window is exposed to the direct rays of the sun, a piece of thin tissue-paper is pasted over the glass, or the glass may be frosted or painted; direct sunlight should never be used except for photomicrography. If an artificial light is to be used, the microscope is placed about thirty centimeters from the light, and to one side, so that neither the heat nor the direct rays from the light will be thrown in the face or eyes of the observer. The best artificial light is afforded by the Welsbach burner or a thirty-two candle-power incandescent burner with a thoroughly frosted globe. While for convenience in general work the stand may be tilted, when examining mounts of liquids, urine, hanging-drop culture, etc., the stand must be upright so that the stage is perfectly level. Place the slide on the stage and loosely secure it by the clips; so adjust the mirror as to illuminate the center of the field; without placing the eye to the eye-piece, rack the objective down until it almost touches the slide; then look into the instrument and perfect the illumination by adjust-

ing the mirror again, if necessary; slowly focus *upward* by the coarse adjustment until a satisfactory focus is obtained; in moving the slide about, the fine adjustment alone is required. *Never* focus downward until you have mastered the method just given; careless, or even at times the most careful, downward focusing will crush the slide or the lens by passing over the true focus and jabbing the objective into the slide. Before removing the slide, always rack the objective upward until it is at least 1 cm. from the slide.

To use the $\frac{1}{12}$ inch oil-immersion objective: First, *with a lower power*, accurately center some object in the field upon which to focus; rack the tube upward until the objective is four or five centimeters from the slide; rotate the nose-piece so that the $\frac{1}{12}$ inch objective drops into the optic axis of the instrument. Erect the stand so as to make the stage level. Place on the cover-glass a drop of cedar oil, at such a point that when the objective is racked down it will touch the drop of cedar oil at its center. The objective is now lowered into the cedar oil; looking into the instrument, adjust the light so that the field is well illuminated, the light uniformly distributed, but not too brilliant or glaring; this, if present, should be overcome by closing the iris diaphragm until a soft, even illumination is obtained. Now, with the fine adjustment, slowly focus upward but one or two turns of the milled head; the object should come into view. If it is indistinct or hazy, try readjusting the iris diaphragm or the light, or the Abbe condenser may be moved downward or upward until the desired effect is secured. In examining stained preparations the iris diaphragm is kept open; for unstained specimens it is choked down, admitting but little light. *The successful study of any specimen is largely dependent upon securing perfect adjustment of all parts of the microscope, and particularly the illumination.* In case the field fails to clear up after careful adjustment of the instrument, examine the lenses to see that they are not dirty.

PART II.

GENERAL PATHOLOGY.

PART II.—GENERAL PATHOLOGY.

INTRODUCTION.

Pathology bears the same relation to a proper study of disease that physiology does to a knowledge of those complicated phenomena the sum total of which is called life. Physiology deals with the normal processes,—the functions of organs and tissues in health,—while pathology is a study of the causes and manifestations accompanying disease. Physiology is the science of normal life; pathology is the science of abnormal life—disease. It has been said, and quite truly, that pathology is morbid physiology—the physiology of disease. The two subjects demand associated study, as from a knowledge of one is acquired more or less information bearing either directly or indirectly upon the other. A detailed study of the intricate problems of morbid processes, and of the relations of tissue change to alteration of function, and a thorough acquaintance with the normal, render at once apparent the intimate association of pathology and physiology.

Throughout the study of pathology it is to be remembered that the changes contemplated are but perversions of the normal. Disease, with its alterations in structure and function, is not an entity from without, not an importation whose existence within the body is passive, but all morbid processes, while they may arise from causes acting from without,—causes having an existence as a part of the outside world properly so called,—are themselves essentially but perversions of normal vital activity. The same cells, or their progenitors, active in a morbid process, were the essential elements in the normal life of some tissue of the body. As the result of altered conditions the cellular activity has been perverted, and the new line of cell life is but a change in the manifestations of cellular activity—not a new, nor foreign, nor extraneous life carried on within the affected tissues. The apparent exception to this, in the growth of animal and vegetable parasites within the tissues, is not really an exception; so long as the life of the normal cells is not in any way disturbed, disease does not result; as soon, however, as the foreign elements interfere with the usual course of events, those cells performing certain functions in a manner recognized as normal for the species under observation assume a new rôle, and manifest their activity along a line foreign to their usual course. It therefore becomes evident that the diseased tissue is the result of changes in the normal, and that the cellular elements present are but modified forms of normal cells. In order properly to appreciate the significance of tissue alterations a careful investigation into the causes of disease becomes an absolute necessity; with advance in the study of **etiology** it has become possible to comprehend many diseases and other phenomena previously inexplicable.

The study of the active process associated with disease and its re-

sults implies the investigation of gross alterations—the **morbid anatomy**; and, what is truly included as a part of the anatomy, the changes in the finer structure of the tissues—the **morbid histology**. That the study of these two divisions of the subject may have important bearing on practical medicine it is necessary to observe the relation maintained between both gross and microscopic lesions and the function of the diseased organ; this constitutes a study of **morbid physiology**, the perversion of the normal, due to, or associated with, the lesions, either gross or microscopic, themselves the active phenomena of disease; and, lastly, the pathologist must be familiar with the results following the subsidence of morbid processes.

In the youth of medicine scientific classification of disease—**nosology**—was even more difficult than now; names were applied because they fitted certain symptoms, little was known as to the intimate nature of morbid processes, and superficial phenomena constituted the basis upon which practically all diseases were grouped. The labels derived from clinical study alone were often totally inadequate and frequently brought into a heterogeneous mass diseases having, possibly, but one symptom in common; thus, for over twenty centuries, decade by decade, the mass of "fevers" has been robbed one by one until each member of the group has been appropriately ticketed and placed in its proper nosologic position. This statement is not to be construed too strictly, lest it smack of finality, and, as Ballantyne wisely observes, finalism is obnoxious to the scientific mind. There can be no doubt that our present conception of many febrile processes must be modified as our knowledge advances; whenever science attains a new height an additional lode is opened and the whole field of view is extended. With the widened horizon old ideas take on new colors and previously mapped areas must again be resurveyed and adapted to newly discovered facts. For these reasons pathology lacks the stability of anatomy, and, like physiology, must frequently readjust itself to freshly acquired knowledge; the theory of air-borne malaria fails as transmission by mosquitos is established, sleeping sickness is transferred to diseases produced by animal parasites, and in the darkness enveloping our knowledge of even syphilis and cancer there is promised light. Investigation constantly extends the boundaries of truth, and the theory of yesterday falls before the revelation of to-day.

The methods of pathologic research by which new truths are acquired must of necessity vary with the morbid process under consideration. When any of the lower animals are susceptible to the disease under investigation, for evident reasons the experimental method offers many advantages. Being able to vary the conditions under which disease is induced in an animal, to kill the animal at any period in the development of the morbid process, and more fully to control external conditions, make this method in many instances of the greatest value.

Like all methods for studying disease, animal experimentation is open to certain objections; it is not possible in all cases fully to interpret the results, or they may not be applicable, on the whole, to man. Again, many diseases to which man is liable can not be induced in animals, and in such cases the method fails. While such important objections to the method often hold true, the author does not recall a single in-

stance in which, after prolonged effort, it has not been possible to learn something, and in a number of diseases the method under consideration has afforded full and entirely satisfactory explanation of phenomena previously obscure or absolutely unappreciated. In many diseases all that is known has been tediously worked out by this form of research. It has been urged that the end attained does not justify the suffering induced in the animal experimented upon. Such an objection need not be answered here, since those who hold it can not know of the advances made by the experimental methods of study, or are not in that condition of mental receptivity necessary to appreciate scientific truths. The results attained by the investigation of disease in lower animals have probably done more to alleviate suffering in them than in man.

Comparative pathology—the study and comparison of morbid processes in the lower animals and in man—also affords ample opportunity to obtain information as to the causes of, and alterations in, disease.

In all pathologic study, to attain the best results the statistical method must be used to a certain extent. The collection of a large number of cases, with a careful analysis of recorded data, can but yield valuable conclusions. The constancy of associated lesions—as, for example, the association of certain nervous and nutritive phenomena with removal or disease of the thyroid gland—often indicates a path for investigation that may terminate in a happy solution of some obscure problem.

The study of diseased organs or tissues postmortem or after operative removal from the body need hardly be mentioned as a most fruitful source of knowledge concerning morbid processes.

In addition to the above methods, it can not be an error thoroughly to study morbid processes during life. Therein lies the strength of the science. The symptoms of a disease are but expressions of the lesions—the morbid physiology induced by chemic, mechanical, or structural alterations. From symptoms it is possible in many cases to infer the character of the tissue changes, or, by studying the alterations in the normal chemistry and structure, the symptoms may be explained. He is far at sea who believes that the study of pathology begins and ends with the postmortem.

CHAPTER I.

THE ABNORMAL; MALPOSITION; MALFORMATION.

General pathology comprehends those variations in structure and function that may attack any organ. It is the study of morbid processes independent of their location, while **special pathology** is the study of diseases of organs independent of the same disease occurring elsewhere than in the organ under consideration.

In order to appreciate the **abnormal** it is necessary to have some definite idea of the normal. Information with regard to health is obtained by studying individuals or organs not manifesting disease and considering as **normal** that condition which is commonest. Difficulty is encountered in accurately judging the limitations within which modification of structure and function may be regarded as physiologic. In most instances, however, the morphologic and physiologic boundaries of the normal are sufficiently circumscribed to permit a ready recognition of conditions that pass beyond their domain. Any deviation from the normal must be recognized as belonging to the **malpositions, malformations,** or **diseases.**

MALPOSITIONS.

Malposition is misplacement of an organ from that position in which it is most commonly found, or any alteration of its relation to other organs; it is a mal-posed structure. The heart may be rotated on its axis and not occupy the normal relation to the surrounding tissue, and still the heart may be in place; so that malposition implies either that the organ is not in place, or that, being in place, its parts do not bear their normal relation to adjacent structures themselves normally located.

Congenital malposition may consist in the perpetuation of fetal characters, and not infrequently is associated with malformation; thus, failure in closure of the body cleft anteriorly, particularly at the umbilicus, may permit a viscus wholly or in part to lie outside the abdominal cavity; fenestra in the diaphragm may allow the heart to descend into the abdomen or one or more abdominal organs to rise into the thorax (congenital diaphragmatic hernia). Organs that develop in one position and later normally acquire another may, for some reason, fail to make the requisite migration and persist through adult life in a position more or less normal in the embryo; a kidney may from this cause lie near the median line or the testicle remain in the abdomen. An interesting form of congenital malposition is that represented by **ectopia** of parts of organs, although the term is also used for entire organs occupying abnormal positions. Some organs show the most extraordinary ten-

dency to *partial* or even *complete ectopia;* thus adrenal tissue may be found in the liver, spleen, neighborhood of the ovary or testicle, and is not infrequently present in the kidney, usually the cortex. Aberrant pancreatic lobules occur in the stomach, duodenum, jejunum, and less frequently in the ileum; gastric glands may be present in the duodenum or in the esophagus; fragments of thyroid may be distributed along the course of the thyroglossal duct, at the base of the tongue, or within the thoracic cavity. The cause of these various forms of ectopia is more or less obscure; the usual explanation, that they depend upon incarceration of growing cells in abnormal localities, is little more than a restatement of the primary facts. It should be remembered that such ectopic tissues are particularly prone to manifest tumor formation; misplaced testes not infrequently become sarcomatous or carcinomatous; lingual, tracheal, and mediastinal goiters develop from ectopic thyroid tissue, and the relatively frequent tumor called a hypernephroma is the result of neoplastic activity in ectopic adrenal tissue.

Congenital malpositions may correct themselves or be corrected by the surgeon, although their tendency is to persist; an umbilical or inguinal hernia of congenital origin may be replaced, an abdominal testis may, by operative procedure, be brought to its normal position; a mesial kidney or a right-sided heart of congenital origin will probably never occupy the position of the normally posed organ.

Acquired malposition may result from congenital defects, disease, trauma, etc. Imperfect closure of the abdominal parietes at the umbilicus, inguinal or femoral outlets, permits the occurrence of hernia at these points; when the muscle of one-half of the diaphragm fails to develop, the absence of contractile power, the elasticity of the lung, and the higher abdominal pressure lead to eventration, the diaphragmatic arch of that side rising almost to the apex of the thorax, permitting abdominal organs to lie within the chest cage but not in the thoracic cavity.

Disease may in a number of ways cause malposition; enlarged organs may by their increased bulk or weight drag from normal attachments; this is especially true of the spleen, kidney, and stomach, and to a lesser degree of the pancreas, transverse colon, and gall-bladder. Disease may also alter the lines of pressure and displace organs not themselves diseased. The heart is pushed to the left and the liver displaced downward by gas or fluid accumulations in the right pleura or massive solid or cystic growths involving that structure or the lung, Acquired malposition may result from loss of normal support by retentive structures. Wasting of the abdominal wall favors prolapse of the contained viscera (visceroptosis). The alteration in pressure throws unusual stress upon the structures normally retaining liver, spleen, and kidneys in place, as a result of which change these organs are prone to prolapse. Loss of support in the pelvic floor permits of uterine displacements. Organs may be pulled out of place by the contraction of fibrous tissue. In chronic interstitial pneumonia when the involved lung is firmly attached to the chest wall contraction of the newly formed fibrous tissue tends to pull the heart and other mediastinal tissues toward the affected side. Inflammatory conditions may perpetuate malpositions due to other causes; adhesions may render reducible hernias irreducible or may eventually bind in its new position an organ but tempo-

rarily displaced. One organ wandering from its normal position may lead to displacement of another; the prolapsed spleen may carry with it the tail of the pancreas; the transverse colon displaced downward may drag upon the stomach and the dilated or prolapsed stomach may in turn displace the colon.

Trauma may in a number of ways give rise to malposition; falls with sudden arrest, or blows in the renal region may loosen normal attachments and be followed by displacement of the kidney. Wounds in the abdominal wall may cause hernia primarily, or secondarily by imperfect healing and relaxation of the cicatrix. Malpositions due to fractures of bone and misplacement of fragments, or dislocation of articular surfaces—constituting both a malposition and an abnormal formation—are usually referred to as deformities, although to the layman malposition, malformation, and deformity are essentially the same.

It will be recognized from the foregoing that malposition, of itself does not constitute disease. Misplaced organs may be functionally normal; removed from the body, a right-sided heart may differ in no respect from a normally placed organ. As already intimated, ectopic tissues are prone to disease, and frequently manifest more or less perversion of function; it is usually maintained that abdominal testes produce no spermatozoa. In most other organs, however, function is manifestly adequate. Malposition not infrequently subjects the affected tissue to influences not exerted upon the same organ in its normal position; the floating spleen, kidney, or liver is more liable to injury than a normally placed organ. Abnormal position not infrequently subjects nerves, vessels, and ducts to unusual stress; traction on the splenic pedicle obstructs the vein and favors congestion, torsion of the pedicle may arrest the circulation. The ureter of a floating kidney is not infrequently compressed, angulated, or kinked, thereby impeding the outflow of urine.

MALFORMATIONS.[1]

Malformation is a deviation in structure and development from that most commonly found. A malformed structure is not necessarily diseased,—although it may have resulted from disease and may manifest a tendency to various pathologic processes which properly may be called diseases. Acquired malformation is commonly called deformity, although the liver distorted by the corset is usually termed a malformed organ. In some ways maldevelopment is preferable to malformation; the former term is usually applied to abnormal conditions depending upon developmental errors, and as most malformations properly so called have this origin, the two terms tend to become essentially synonymous.

Teratogenesis.—While the causes of malformation may, in certain instances, be evident, a large percentage of cases are inexplicable by any facts at present in our possession. It must be apparent that any essential abnormality in germ or sperm cell, or both, necessarily tends to abnormality in the evolved product of their union. Abnormal influences brought to bear upon the impregnated ovum must necessarily

[1] Consult Ballantyne, "Manual of Antenatal Pathology and Hygiene," "The Embryo," 1905.

modify its growth. It is therefore apparent that certain causes may be regarded as *intrinsic*—having their origin in the cells from which the new being springs; other causes are extrinsic, depending upon influences acting upon what might be called a normally disposed developmental process. An important member of the intrinsic causes is inheritance; web-fingers (syndactylism), short, stunted fingers or toes (perodactylism), harelip, and minor abnormalities are frequently transmitted by one or the other parent. A mother may bear normal children by one husband while by another the offspring may show malformations transmitted by the father. When a malformation is traceable to a remote rather than an immediate ancestor, the condition is called *atavism*, or reversional heredity. Closely allied to the transmission of gross morphologic defects must be classed the undemonstrable cellular or cytochemic peculiarities of tissue which create tendencies to disease or abnormal susceptibilities, to which reference will be made later.

In the chick it has been demonstrated that such external influences as temperature change, shellacing the egg, frequent shaking, and abnormal posture may determine malformation in the offspring. The human embryo in ectopic pregnancies is not infrequently malformed. Abnormal pressure upon and abnormal position of the extremities may modify the shape of the bones and soft parts. Insufficient amniotic fluid especially subjects the fetus to external influences. Adhesions between the embryo and the amnion and abnormal pressure exerted by the membrane may also be causes. Pressure exerted by the hand and chin on the thorax may interfere with development of the sternum. The funis wrapped around an extremity may by pressure cause amputation. It has been alleged that increased abdominal or uterine pressure may produce malformations; Ballantyne does not hold this view, nor does he look with favor upon the often expressed opinion that malformation of one twin may be due to pressure exerted by the other. These and similar influences are called the *extrinsic* causes of malformation. The earlier these influences become operative, as a rule, the more marked the resulting malformation.

Nosologic or Pathologic Theory.—Disease of the fetus may give rise to important developmental defects. Obliterative changes in the fetal vessels may arrest or modify the development of the affected tissues; thus occlusion of the renal artery may prevent or arrest the evolution of the kidney, and endocardial lesions causing stenosis of the pulmonary artery may indirectly prevent perfect closure of the ventricular septum. Not only may the fetus be influenced by its own diseases, but morbid processes (for example, infections) in the mother may exert a deleterious action on fetal growth.

The Embryologic Theory.—It is recognized that in many malformations there is little more than perpetuation of normal fetal conditions; fissures in the median line, whether complete or incomplete, anterior or posterior, are more or less perfect perpetuations of developmental features. While recognizing these facts, difficulty still remains in explaining why the normal developmental process was not completed. The abnormality may have been influenced by heredity, the fusion of abnormal ova and sperm cells, abnormal pressure, amniotic adhesions, intrauterine injury, or other causes.

No satisfactory classification of malformations can readily be made.

Minor abnormalities are usually called congenital malformations; gross and conspicuously altered individuals are termed monsters. When but one individual is affected, it is called a single malformation or a single monster—**monosomatous terata**; the terms double malformation and double monster are applied when two or more fetuses are involved—**polysomatous terata.** Malformations following a uniform type are called typical, while those assuming irregular forms are called atypical; the latter do not yield to any ideal systematic classification.

Ziegler recognizes five groups of single malformations:

(1) Developmental arrest (**monstra per defectum**), which would include agenesis or aplasia—absence of an organ or part—and hypoplasia—imperfectly developed organ or part. With this group would also be included fissures and clefts in the median line, both anterior and posterior, due to the imperfect development, faulty or non-union of extensions that normally meet in the median line. Cranial defects belonging to this class I have described under malformations of the central nervous system, and facial abnormalities involving the upper respiratory and alimentary tracts with those systems. Other fissures in the median line anteriorly may affect the thorax (**thoracoschisis**) or the abdomen (**fissura abdominalis** or **gastroschisis**) or both (**thoracogastroschisis**). Such malformations may be associated with the eventration of one or more organs normally enclosed within the cavities affected. In lesser degrees (**fissura sterni, fissura abdominalis incompleta**) the cavities are enclosed although the walls in the median line are more or less weakened. Affecting the urinary organs, imperfect union in the median line may give rise to fissure or exstrophy of the urinary bladder, and, when projected downward, genital fissure and epispadias.

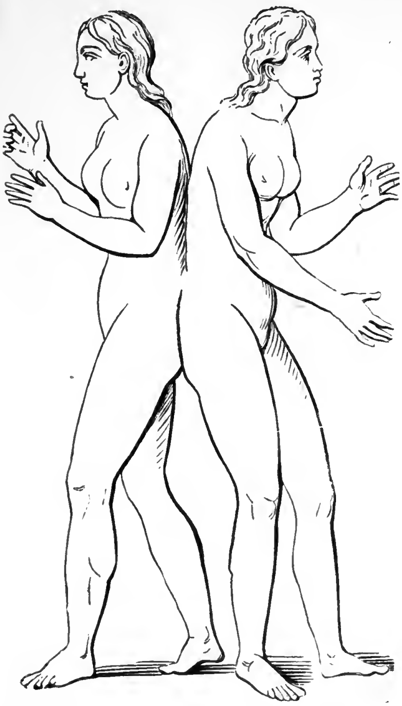

FIG. 49.—PYGOPAGUS.—(*Debierre, Simes' translation.*)

(2) When the growth exceeds the normal (**monstra per excessum**) the affected structures are increased in size or number, or both. With this group would be included partial giant growth, general giant growth, and accessory and supernumerary structures.

(3) Congenital malposition of organs (**monstra per fabricam alienam**) is represented by a situs transversus (see malpositions of heart, stomach, liver, spleen, etc.).

(4) Persistent fetal structures that normally disappear, as, for

example, the thyroglossal duct, the persistence of which may cause cysts (see malformations of the thyroid gland), or the omphalomesenteric duct (see malformations of the intestines).

(5) This group includes true and false hermaphroditism. True hermaphrodites are bisexual, false hermaphrodites unisexual. In **hermaphrodismus verus** testis and ovary are present. In **pseudohermaphrodismus** various combinations of the male and female characteristics may be present, the true sex depending upon which sexual glands are found in the individual.

The double monsters (**monstra per duplica**), or, according to Ballantyne's classification, **polysomatous terata,** are instances in which two or more individuals are involved. This group includes monochorionic or homologous twins, and also triplets, quadruplets, quintuplets, all of which in man, according to Ballantyne, should be classed with the terata. When the individuals communicate with each other by the umbilical vessels in or near the single placenta, they are said to be allantoido-angiopagous twins; usually one is deformed. When the twins are so joined that some parts are structurally continuous, they are called duplicated monsters or double terata, which may be symmetric,—that is, both approximately equally developed,—or asymmetric, in which case the rudimentary or imperfectly developed individual is said to be a parasite, or parasitic upon the other. When the individuals are joined together posteriorly, the anterior parts are said to be duplicated (**duplicitas anterior**). In the **pygopagus** the coccygeal or sacral areas are fused. In the **ischiopagus** the pelves are fused end to end, the sacra being apposed. In the **dicephalus** the trunks are fused, the heads alone or the heads and necks more or less clearly separated. When the heads alone are fused (**craniopagus**) the fetuses may be joined end to end (**craniopagus parietalis**), the anterior parts may be merged (**craniopagus frontalis**), or the junction may be in the neighborhood of the inion (**craniopagus occipitalis**). When the anterior parts of the body are more or less perfectly fused, the condition is called **duplicitas posterior.** With more or less perfect separation of the trunks and fusion of the heads the **syncephalus** results. In the **dipygus** only the lower half of the trunk and extremities are duplicated. Lateral fusion (**duplicitas parallela**) is rare. Among the commoner forms of double monster are the **xyphopagus,** in which union occurs at the xyphoid; a more extensive union in the breast-plate is called a **sternopagus ;** both these forms are included in the group **thoracopagus.**

CHAPTER II.

DISEASE.

The fact that the normal for any given function is bounded by relatively widely separated extremes renders it difficult to formulate a definition for disease that will at all times fall within the scope of morbid manifestations. To say that disease is any tissue alteration, chemical or structural, altering the function of a tissue or an organ, such limitations being beyond the extremes of the normal, rather obscures than clarifies our idea of the condition. Chantemesse and Podwyssotsky define disease as the sum of the actions and reactions provoked in the function, structure, and harmony of the organism by a morbid cause. The changes produced by disease are its lesions; the alterations in structure, its morbid anatomy; the symptoms, its morbid physiology; permanent tissue alterations are its results. It has been the custom to speak of **organic disease,** implying thereby disease of structure or structural alteration, evident to the unaided eye (macroscopic lesion) or demonstrable with the microscope (microscopic lesion). Of the chemical alterations in tissue we know much less; it is evident, however, that structural changes have a chemical basis and are associated with an abnormal chemistry in the tissues involved. The fact is shown by the increased collagen of fibroid organs, the abnormal oil content in fatty infiltration and fatty degeneration, the apparently newly formed substance in lardaceous disease, and the manufacture and deposit of abnormal pigments in certain types of the pigmentary infiltrations; with the more subtle chemistry of many abnormal processes we remain indifferently acquainted.

In most diseases an anatomical basis—more or less constant alteration in particular tissues—can, by the means at present at our disposal, be recognized. There is, however, a relatively large list of morbid manifestations possessing no demonstrable tissue alteration. These are called **functional diseases,** and include such clinical phenomena as palpitation of the heart, certain types of vertigo, hysteria, neurasthenia, and a number of the insanities. Improved technic and more extended study are constantly narrowing the realm of functional disease, and it is generally recognized that the term is a cloak for our ignorance but expressing the limitations of our knowledge. The most reasonable explanation of these obscure diseases is the hypothesis that they depend upon chemical alterations in the affected tissues or are responses to the influence of unidentified poisons acting upon cells and inducing abnormal manifestations without at the same time giving rise to recognizable structural alterations.

The limitations of our knowledge are such as to render accurate **nosology** (the scientific classification of disease) more or less imperfect; a classification based upon cause at once encounters numerous diseases the causes of which are unknown; if we turn to structural change, the

fact confronts us that, in some instances, apparently identical lesions are produced by different causes. Symptomatology offers us nothing better, and hence at present the nosologist is driven to the acceptation of a veritable medley in which the strains of all possible bases of classification may be recognized.

With regard to the duration of disease the terms acute and chronic are usually applied. **Acute diseases** are manifested by suddenness of onset, relatively short duration, possess fairly constant characters, are not infrequently self-limited, and usually are marked by a frank symptomatology. **Fulminating, foudroyant,** or **hyperacute diseases** are characterized by suddenness and intense severity.

Chronic diseases begin insidiously, frequently imperceptibly, although occasionally they are the perpetuation of acute attacks. They are further characterized by a rather indefinite duration, irregular or varying symptoms, which not infrequently intermit or remit; the lesions may or may not be accompanied by remission or intermission; commonly the latter are uninterrupted, although the rapidity of advance often varies.

Diseases due to parasites are called **parasitic diseases**; ordinarily the use of the term is restricted to morbid processes due to animal parasites. Diseases due to lower forms of vegetable life are called **bacterial, microbic,** or **germ diseases**; an infection evidently due to a living contagium and without which the morbid process cannot occur is called a **specific disease.** Diseases readily transferred from man to man, or from animal to man, are called **communicable**; those of the communicable diseases transmitted by contact, mediate or immediate, are termed **contagious.** Diseases due to the entrance and proliferation of a vegetable organism in the tissues of the body are also called **infections** or **infectious diseases.** Morbid processes for which we can discern no adequate cause are called **idiopathic**; rather than say idiopathic or of "self-origin" it would be better to use **cryptogenic,** meaning of hidden or obscure origin.

A disease constantly present in a given area is said to be **endemic**; when occurring only occasionally, **sporadic.** When a large number of cases occur in a single locality, in a brief period, the disease is **epidemic**; when an epidemic is distributed over a larger area,—*e. g.*, a hemisphere,—it is called a **pandemic.**

Traumatic diseases are due to injury. When the cause enters by the alimentary tract, the disease is said to be of **ingestive** origin.

It is often convenient to divide diseases into local and general, the former restricted to some particular organ or area and the latter showing a much wider distribution. Systematic writers, for convenience in description, not infrequently classify diseases on an anatomical or regional basis; thus surgeons write of surgery of the head, the internist of diseases of the pulmonary system, the gynecologist on affections of the reproductive organs, and neurologists on diseases of the nervous system.

Complications are morbid conditions not usually constituting a part of the disease with which they occur but traceable to its manifestations; thus, perforation of the intestine is a complication of typhoid fever resulting from extension of the necrotic process in the typhoid ulcer through the intestinal wall. They differ from **intercurrent diseases,** which attack a patient already the victim of some other affection.

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Sequelæ are morbid processes which ordinarily do not develop until the patients have almost or quite recovered from the diseases to which they are due. The distinction between sequel and complication is not always clear; a nephritis occurring during the course of scarlet fever is a complication; appearing later, a sequel.

Pathogenesis or **etiology** is that branch of pathology dealing with the cause of disease. Whatever may be the change going on in an organ or tissue, it must be recognized that there is some underlying cause, and that the recognizable manifestation is the reaction of the structures to some influence the exact character of which may not be known. White defines a cause as the invariable, unconditional antecedent of an event, which, in relation to the cause, is called the effect. In pathology the factor or factors giving rise to disease constitute its cause; the alterations in structure and function, the effect. No satisfactory classifications of causes can be made, although general subdivisions are recognized.

Predisposing, remote, or **conditional** causes are those favoring the action of the **immediate, unconditional,** or **exciting** causes. Surgeons have demonstrated that tissues may be injured without the occurrence of suppuration; the essential cause in the production of suppuration is infection. The wound, by breaking the continuity of a protected surface, injuring the tissues and introducing bacteria, indirectly causes the subsequent inflammation and suppurative processes. Predisposing causes are not specific, exciting causes partake more of this quality.

There are certain causes that are inherent to the individual; these are called **internal, intrinsic,** or **autogenous.** Among this group should be mentioned **age.** Some diseases are largely restricted to infancy; others to adolescence, adult life, or old age. In the influence exerted by age on the inception of disease a number of special features must be recognized. The fact that in infancy and in youth the body is first exposed to certain infectious diseases which, if once acquired, do not recur, renders those affections common during that period in life not because of any overwhelming susceptibility incident to the age, but rather because the initial exposure happens at that time. There can be no doubt, however, that the child is more susceptible than the adult to certain infections, for example, scarlet fever, diphtheria, and infections of the alimentary canal. The susceptibility of young bones to infection during the period of adolescence is probably attributable to the vascularity of active growth and the frequency with which injury occurs at that time. During adult life the individual is subjected to the dangers of the heightened activity incident to the period, and with old age come lesions of the vessels and failing functional activity in a number of tissues—especially the renal and cardiovascular systems—which in time bring perils of their own.

Sex influences the occurrence of disease not alone because of anatomical and physiologic differences, but to a large degree on account of difference in habits. The fact that the mammary gland in the female is functionally active through a large period of a woman's life renders it particularly prone to disease, while in man the organ is rarely affected; the short urethra of the female renders her infrequently subject to vesical calculus. Man falls a victim to diseases favored by

exposure, for example, pneumonia, rheumatism, and sunstroke; woman, as a result of her immured existence and consequent deprivation of fresh air and sunlight, is especially liable to anemia. The lax sexual life of the male makes him the frequent subject of venereal disease and his less restrained appetite brings the dangers of intemperance, especially alcoholism.

Race.—The negro is less susceptible to malaria than the Caucasian, but is a great sufferer from tuberculosis in all its forms. Chorea is rare or unknown in the Mongolian.

Idiosyncrasy is an unusual susceptibility to the injurious action of agencies that do not influence other individuals. Some persons are peculiarly susceptible to fish or mushrooms, certain odors, or particular medicaments, especially the iodids, opium, or quinin.

Among the most important of the intrinsic causes of disease is **heredity.** It is generally agreed that there is no essential difference between physiologic and pathologic heredity. Certain diseases seem to be essentially the results of heredity. Important among these can be mentioned the hemorrhagic diathesis and Friedreich's ataxia, both of which are discussed elsewhere. Woods Hutchinson in 50,000 cases of insanity found hereditary influences operative in 22.6 per cent.; McGugan thinks that in America hereditary tendencies are present in 80 to 90 per cent. of the cases. It is not possible in this work to enter into a discussion of the inheritance of acquired characters, but there can be no doubt that the product of conception is materially influenced by acquired processes affecting the parents. The frequency with which tuberculosis attacks those of a certain ancestry, and the tendency of the offspring of syphilitic parents and those addicted to chronic alcoholism to certain diseases, must generally be admitted. It seems well established that the mother is more likely to transmit than the father. Various explanations have been offered for the high mortality of certain diseases among the progeny of alcoholics and syphilitics. It seems highly probable that poisons circulating in the blood of a parent may influence the developing sexual cell, rendering the offspring more susceptible to certain diseases. Noxious influences are more prone to exert their deleterious action upon highly organized tissues, and more especially upon structures whose highest physiologic action has been last acquired in the evolution of the race. If this view be correct, it satisfactorily explains the frequency with which disease of the nervous system attacks the progeny of alcoholics, syphilitics, and those suffering with chronic lead-poisoning, and other intoxications.[1]

The presence of one disease may predispose to another; leukoplakia of the tongue may terminate in cancer; diabetics are especially susceptible to certain infections, and patients having chronic interstitial nephritis are more liable to inflammation of the serous membranes. This increased susceptibility to some other disease is probably the result of the deleterious action of the existing process on the normal inhibiting influences of the body.

The **external, extrinsic,** or **exogenous causes** of disease are those factors acting upon the body from without. Some of these are in a way special; others may be regarded as the sum total of man's environ-

[1] For bibliography of heredity in its relation to pathology see Chantemesse and Podwyssotsky, "Les Processes Généraux," vol. i, p. 93.

ment. Certain diseases are restricted to warm countries, because in such climates only are conditions suitable for their propagation. Those diseases propagated by insects cannot occur in regions the climatic conditions of which preclude the existence of suitable insects. This is especially borne out by our knowledge of trypanosomiasis and malaria. The influence of climate on disease is also shown by the occurrence of seasonal exacerbations in certain affections and the fact that some diseases are particularly frequent during certain months. Cleemann found that of 621 cases of typhoid, 441 occurred during the summer and autumn. Smallpox is most active between December and February; pneumonia is twice as frequent in the winter and spring as in the summer and autumn. That man tends to adapt himself to climatic influences is shown by the heightened susceptibility to tropical diseases manifested by the unacclimated.

Certain **occupations** are so constantly associated with definite processes that the latter have been called artisan's diseases; those brought in contact with lead suffer a special type of intoxication called plumbism. Laborers in dust-laden atmospheres acquire pneumonoconiosis; the pen and the telegrapher's key induce writer's cramp and telegrapher's cramp respectively.

The **habits** of the individual may subject him to special dangers. Smoker's cancer follows the local irritation of pipe or cigar and certain cardiac and nervous phenomena may result from the absorption of poisons derived from tobacco. The deleterious effects of alcoholic intemperance are well known. Mention may here be made of the so-called **mental causes,** among which should be classed prolonged mental effort, anxiety and worry, and the depressing influence of profound emotion. The prevalence of certain diseases of the nervous system is directly attributable to the great strain which the modern life throws upon the nervous system.

Starvation and Allied Conditions.—The inability of the body to secure the materials requisite for the maintenance of function, including growth and replacement of waste, is followed, more or less rapidly, by well-marked disturbances. Deprivation of the elements requisite for nutrition may be dependent upon external conditions, or may, to a certain extent, arise from perversion of normal processes. Thus, the cutting-off of oxygen may be dependent upon its absence or scantiness in the surrounding medium, as when the body is submerged in water, or it may be due to occlusion, to spasm, or to the presence of a foreign body in the air-passages; or, as a result of altered absorbing power, the blood may not be able to take up the gas even when the latter is abundantly supplied in the vesicular structure of the lungs. In carbon monoxid poisoning the gas seems to combine so firmly with the oxygen-carrying bodies that it can not be displaced, and no matter how rich in oxygen the inspired air may be, it is not absorbed as in health. The changes induced are largely dependent upon the extent to which the supply is diminished, the duration of the oxygen starvation, and the facilities afforded for the excretion of materials the accumulation of which is favored by the absence of the normal respiratory interchange. If the amount of oxygen supplied be but moderately diminished, the most frequent changes occurring in the fluids and organs of the body are degenerative processes. so slowly brought about

as to be inconspicuous until in an advanced stage. The more marked or more rapid lessening of the supply of oxygen, such as results from pressure of exudates or tumors without the larynx or swelling within, gives rise to the condition known as asphyxia. In the production of the phenomena grouped under this heading the accumulation of carbon dioxid has probably more, or certainly equally as much, to do, as the associated diminution in the quantity of oxygen present.

Food and drink, as well as oxygen, are necessary for the maintenance of life, and a marked reduction in the supply of any of these will be associated with evident changes in the nutrition of the organism. As is the case with oxygen, so we find with food: the intensity of the lesions produced depends largely upon the extent and rapidity with which the food-supply is reduced. Insufficient nourishment usually gives rise to lessened resistance on the part of the individual, rendering him more susceptible to the action of causes that, under ordinary circumstances, would produce no effect. With the complete withdrawal of food and water there is rapid combustion of the fats of the body, associated with the destruction of the proteids and the rapid loss of water. The tissues whose functions can be best spared suffer most; in prolonged starvation Voit found that the weight of the brain and spinal cord diminished three per cent. while the fatty tissues of the body lost ninety-six per cent. This fact is supported by the early utilization of the fat, by the progressive wasting of the skeletal muscles, and by the fact that the heart, kidneys, and nervous system are the last to suffer and are the least altered. Parenchymatous changes are observable in nearly all the organs, and toward the last these changes may become marked in organs the function of which is absolutely necessary for the maintenance of life. In addition to the absence of food and the fact that the body must, in a certain way, consume its own tissue to maintain heat and to supply the force requisite for carrying on respiration, circulation, etc., there is also an accumulation within the body of poisons that tend to induce disintegration of the tissue elements.

Ordinarily, the occurrence of starvation is dependent upon the inability of the organism to obtain food; but occasional instances occur in which as a result of degenerative lesions of the mucosa of the alimentary canal, and from other causes, the power of the organism to digest or to assimilate available pabulum is lost, and death occurs as a result of starvation, although abundant food is supplied. Starvation may result from more or less marked occlusion of the esophagus by stricture, tumors, etc.; under such conditions, before the advent of modern surgery, cases of starvation were occasionally observed. As before indicated, starvation may be dependent upon lesions of the secondary as well as of the primary assimilative forces. Thus, in certain blood dyscrasias the error of assimilation seems to be not in the digestive organs, properly so called, but in the power of the system to utilize the material supplied.

Food supplied to the body or to an organ is utilized for replacing waste, for maintaining growth, when this is necessary, and for the continuance of other functions. If an organ be called upon to accomplish more work than is possible with the food available, it is overworked, and the results of this overwork become at once manifest. These are not unlike the alterations dependent upon scanty or inadequate food;

in fact, the two conditions are essentially similar. An organ doing little or no work utilizes but little pabulum; on the other hand, a greatly overworked organ may demand more nutrition than may be available, or the very fact that it is manifesting excessive functional activity may lessen its power to assimilate the nourishment supplied. In addition to the foregoing, nourishment of an organ is dependent not only upon its reception of the required amount of food, but also upon its ability to throw off the products of its own activity. An organ greatly overworked may be so situated as to permit accumulation in its interior of one or more poisons the presence of which exerts a deleterious influence upon the cellular elements of its own tissue. As an example of this form of exhaustion, which is really but another name for starvation, may be mentioned the important structural lesions noted by Hodges in the ganglion cells of pigeons. It has been said that tissues are not nourished, they nourish themselves; for the proper execution of this function food must be supplied, the cell must be able to utilize the pabulum, and removal of effete material must be sufficient; failure in the fulfilment of any of these requirements leads to structural lesions, and thereby to disease.

The **thermal causes of disease** may be grouped under several headings: (1) The local influences of very high and of very low temperatures as applied directly to cutaneous or mucous surfaces; (2) the influence of elevated temperatures upon the heat-coordinating apparatus of the individual; (3) the influence of cold on the structure and function of tissue.

Burns and Scalds.[1]—The character and extent of the local changes induced by exposing tissues to elevated temperatures are dependent upon the tissue, the length of exposure, and the height of the temperature. The more delicate tissues are susceptible to slight rises of temperature, while the palm of the hand and the sole of the foot may be accustomed to withstand temperatures which would be destructive to tissues richer in juices and cellular elements. Comparatively low temperatures—50° C. to 55° C.—may be followed by vesication and necrosis; in individuals whose resistance is depressed by hemorrhage, exhausting sickness, or similar conditions, even lower temperatures may be destructive to vitality. When the temperature is comparatively low,—41° C. to 52° C.,—the length of time of the exposure determines, to a large degree, the extent of the injury. Ordinarily, the local application of temperatures under from 50° C. to 51° C. is not associated with any marked structural change. When, however, temperatures begin to ascend above this point, cell destruction is likely to occur, associated with the formation of exudates of various kinds and with inflammatory processes of varying degrees of intensity.

With regard to the local application of cold, the changes brought about, when the reduction of temperature is sufficient, very closely resemble those produced by high temperatures. The application of liquefied air produces such extensive necrosis that it has been proposed to utilize the agent as an escharotic, exactly as caustics may be applied for the destruction of morbid growths. Rischpler[2] finds that all soft

[1] Bardeen, "Jour. of Exp. Med.," 1897, vol. ii, p. 501; McCrae, "Deut. Zeit. f. Chir.," 1903, vol. lx, p. 469; Vernly, "Rif. Med.," June 17, 1903; Locke, "Boston Med. and Surg. Jour.," Oct. 30, 1902.

[2] "Ziegler Beiträge," 1900, vol. xxviii.

tissues, with possible exception of the elastica, are influenced by freezing; vacuolization and granular changes are most conspicuous; the cells shrink and the nuclei manifest distortion with marked alterations in the chromatin reaction. If the temperature has been low or the exposure prolonged, cell death results.

Attempts have been made to classify burns according to their intensity or the extent of the destruction induced; such classifications must, of necessity, be arbitrary, as all degrees and stages must merge into one another, there being no sharp lines of demarcation. Thus, it is said that *burns of the first degree* are associated with slight hyperemia and followed by a more or less superficial desquamation. *Burns of the second degree* give rise to the formation of blebs, with liquefaction necrosis and exfoliation of a certain amount of destroyed tissue, but not involving all the layers of the skin. *Burns of the third degree* involve the entire skin, and terminate in the formation of eschars composed largely of that structure. *Burns of the fourth degree* imply a still more extensive destruction of the tissues, amounting practically to carbonization.

These classifications are largely concerned with the local influences of the heat, and do not take into consideration the systemic phenomena The latter are dependent more upon the amount of surface involved than upon the degree of the burn. When over one-third of the cutaneous surface is seriously impaired by the burn, the injury is likely to prove fatal. A number of theories have been advanced to explain this well-known fact. When death follows immediately upon the inception of injury, probably the only factor with which we have to deal is shock. When, however, death occurs some time later,—preceded by focal hemorrhages and necroses in one or more organs, particularly in the alimentary canal and liver, and by hematuria, hemoglobinuria, and other evidences of violent intoxication,—it must be evident that we are dealing with something more than shock pure and simple. Among the explanations which have been offered the following may be mentioned:

(1) Suppression of the cutaneous functions of the area involved; (2) perturbed or altered nervous system, the perturbation or alteration being dependent upon reflex phenomena; (3) the formation of toxic substances in the blood; (4) the destruction of blood elements; (5) the absorption of ptomains or other poisons from the injured area. As experimental evidence can be adduced to show that poisons are present in the blood under such circumstances, it may be reasonable to presume that they are influential in bringing about the fatal terminations. Exactly what is their origin or their character must remain for the present an open question. Bardeen has shown that degeneration and areas of necrosis involve the renal and hepatic parenchyma and that the lymphatic tissues throughout the body become edematous and at points necrotic. The lesions observed are strikingly similar to those produced by the poisons of such infectious diseases as diphtheria; he concludes, therefore, that death is the direct result of the toxemia. McCrae regards the changes in the lymph-nodes as proliferative, but of toxic origin. Locke has shown that in severe burns the red cells increase from 1,000,000 to 2,000,000 per cmm., and in fatal cases from 2,000,000 to 4,000,000. Leukocytosis from 40,000 to 50,000 promptly

occurs. The blood is dark and flows sluggishly. As stated by Wilms, the conspicuous excess in erythrocytes is clearly due to concentration resulting from the loss of serum.

As a result of exposure to considerable elevation in the temperature of the surrounding medium, the heat-coordinating power of the body may be altered in a quite characteristic manner, giving rise to the well-recognized condition known as **sunstroke**—a morbid process dealt with elsewhere.

The local application of **cold** induces changes closely resembling those produced by heat. An extremely low temperature in the surrounding medium, aside from the local changes, brings about a more or less gradual reduction in the activity of the body functions, and eventually causes death. Exposure to very low temperatures is slowly followed by reduction of the temperature of the body. When this reduction exceeds about 13° C., death usually results. When the temperature of the body is reduced to 26° C., or possibly a degree or so lower, recovery is possible; after apparent recovery the temperature may rise above the normal, and death, preceded by more or less fever and emaciation, sometimes occurs even at this late period. Fischl has shown that if the temperature of rabbits be artificially reduced by exposing them to cold, the susceptibility of the animal to infections, and particularly the pneumococcus, is notably increased.

The **x-ray** induces well-marked lesions in tissues exposed to its action; the resulting affection may be acute or chronic. The former may be a simple dermatitis or associated with actual necrosis of tissue. Codman found that of 167 cases, 53 were forms of dermatitis, 14 burns of the first degree, 29 of the second degree, and 71 of the third. Some individuals manifest a marked susceptibility to the ray. The prolonged or repeated action of the ray produces a definite tissue necrosis (burn), the affected cells dying, fragmenting, and desquamating, or, when deeply seated, possibly undergoing absorption. It is commonly alleged that most of the influence induced by the *x*-ray is trophic in nature, but, while admitting a possible or frequent trophic action, the fact that excised tissues may be changed by the ray and that neoplastic structures (particularly superficial cancer) and tuberculous tissues, but little subject to trophic influences, are profoundly susceptible to its action, all speak for its necrosing qualities. Some of the effects produced by the ray may be due to endovascular changes—proliferation of endothelium and consequent narrowing of the vessel lumen—lessening the nutrition of the involved tissues.

Trauma as a cause of disease can be little more than mentioned at this point. (See articles on Inflammation and Repair.) Its relation to morbid processes will become more evident as we proceed. As a result of trauma, more or less destruction of tissue occurs, associated with laceration and fragmentation of adjacent or more resistant cells, which, though not actually destroyed by the injury, are no longer capable of resuming active functions, and eventually die and disintegrate. During the absorption and removal of the dead tissue certain poisons are formed the activity of which, in the production of both local and systemic symptoms and lesions, can not be overlooked. Aside from these direct results of wounds, whether the latter be large or small, the possible introduction of irritants, which may further injure the tissue,

must not be overlooked. The irritants introduced by wounds may be microscopic, and of themselves of but little importance: for example, the pigment introduced in tattooing. As a result of the acicular character of certain introduced bodies, such as scales of steel, more extensive cellular alteration may be brought about. Again, these bodies may be poisons, giving rise to extensive degeneration, necrosis, and inflammation, such as is seen in and around the matrices of the nails, or in the skin as a result of injury and the introduction of the cyanid salts used in photography. Aside from the direct destructive influence of injuries and the incidental introduction of inorganic substances, irritant and otherwise, the introduction of infective bodies—bacteria of all kinds—may be mentioned at this point, although they will be more specifically considered in connection with bacteria, and again when treating of wounds, repair, etc. The possible relation of tumor formation to trauma will be considered elsewhere. (See Tumors.)

Alterations in Atmospheric Pressure.—A sudden fall of atmospheric pressure, such as is observed in balloon ascensions and in mountain climbing, may give rise to palpitation of the heart, respiratory embarrassment, mucous and submucous hemorrhage, unconsciousness, and even death.[1] More or less prolonged residence in a rarefied atmosphere may cause an increase in the number of red blood-cells in the peripheral circulation and notably augment the amount of hemoglobin. Many of the symptoms have been attributed to lack of oxygen or to the inability of the blood to absorb oxygen in its more rarefied form, and also to the influence of rapid evaporation of water that takes place under lessened atmospheric pressure.

Laborers in caissons and divers suffer, on their return to the normal atmospheric pressure, from a series of phenomena to which has been given the name **caisson disease.** The incidence of the disease, rapidity with which it occurs, and the severity depend upon the condition of the individual, the ventilation of the enclosed chamber, and the amount and duration of the compression. Under an increased pressure amounting to ten kilo, men usually can work eight to ten hours; fifteen kilo can not, with safety, be withstood over three hours; when the pressure reaches twenty kilo thirty minutes is all that can be borne with safety. The great danger is rapid decompression; if the locking-out be sufficiently slow, no symptoms appear. Crile and Macleod[2] have demonstrated that the symptoms and lesions are due to the presence of gaseous emboli in the capillaries which may rupture and permit the escape of gas and blood into the surrounding tissue. The symptoms come on shortly after decompression, but may be delayed a number of hours. In fatal cases there is marked congestion of the central nervous system and thoracic viscera; inflammation of the lungs has been recorded. Hemorrhages in the spinal cord and clear vacuolated areas are also found; secondary softening and degenerative changes may follow severe lesions.

[1] For bibliography of mountain sickness see article by T. Clifford Allbutt, "Allbutt's System of Medicine," vol. ii, p. 456.

[2] "Jour. of Hygiene," October, 1903, p. 481; see also Fiessler, "Deut. Arch f. klin. Med.," 1904, Bd. 81, H. 5 and 6; Aldrich, "Medical News," November 26, 1904, p. 1020. See also Lie. "Virchow Archiv," Bd. 178, p. 142, on "Changes in the Central Nervous System."

Electric discharges as causes of disease and death have assumed considerable importance since the wide-spread introduction of electricity. The burns produced by electricity manifest nothing peculiar or characteristic, with the possible exception of vagaries in distribution. As a rule, the phenomena induced by electric discharges are most marked in intensity at the time of their occurrence, and rapidly disappear; only in rare instances do they persist. The effects of electric shock are, of course, dependent upon the intensity and duration. After *lightning-stroke* the clothing is frequently found torn, and sometimes distributed in fragments some distance from the body. The foot covering, probably by reason of its immediate contact with the earth, and possibly as a result of changes in its conductivity and of irregularity of moisture in its interstices, commonly suffers most.

FIG. 50.—MARKS PRODUCED BY LIGHTNING.—(*Ziegler*.)

Aspinall,[1] Jellinek,[2] Crile and Macleod[3] have especially studied injuries and death due to electricity. Jellinek refers to an instance in which 95 volts, under extremely advantageous conditions, caused death, and another in which recovery followed a shock by 5500 volts. It is generally believed that alternating currents are more dangerous than direct, although with this view Aspinall does not agree. According to this observer, 600 volts require abnormally favorable conditions in order to prove fatal. Jellinek is of the opinion that exposure to a current of 100 volts requires precaution, 200 volts may be dangerous, and 500 volts can prove fatal. The direction of the current through the body is important; Aspinall believes the left side more vulnerable than the right. Some individuals are much more susceptible than others and the same individual does not always show equal resistance. Aspinall holds that during sleep severe shocks are well borne; idiots are quite tolerant to high voltages. At postmortem lesions may be difficult to recognize, and occasionally are microscopic only; the brain and membranes usually show hyperemia and hemorrhages which may be macroscopic or microscopic and are usually most marked in the gray matter. The cerebrospinal fluid is increased and there is congestion of the internal organs, especially the lung, liver, and kidney. Jellinek has described definite changes in the ganglion cells of the brain and cord, manifested by chromatolysis, tigrolysis, displacement of the nuclei, abnormal cell contour, and swelling of the axis-cylinders. These lesions account for the paralysis and ner-

[1] "Lancet," March 8, 1902.
[2] "Lancet," Feb. 7, 1903, p. 357; also "Virchow Archiv," Bd. 170, H. 1.
[3] "Amer. Jour. of the Med. Sciences," March, 1905, p. 417.

vous phenomena that sometimes follow lightning stroke and other electric injuries. Spitzka in the study of a criminal killed by electricity noted a marked postmortem rise in temperature.

Among the most important causes of morbid processes are substances ordinarily designated **poisons.** The old idea of a poison was something introduced from without, entering the body by way of the alimentary canal, respiratory organs, skin, or genito-urinary system. With pre-formed poisons of the foregoing type the toxicologists and students of legal medicine particularly have to deal. An extended knowledge of physiologic and pathologic chemistry, and a more intimate acquaintance with morbid processes, have led to the recognition of an entirely different group of poisons having their origin within the body, some of them the product of tissue cells. The resulting enormous extension of the field covered by the term poison has led to great confusion and more or less ineffectual attempts at satisfactory classification; much that was old had to be set aside or readapted to new conditions, and the greatest difficulty was encountered in properly bringing together and classifying the newly acquired data. With the pre-formed poisons, entering from without, but little difficulty arose. These were called **exogenous** or **extrinsic,** and were further subdivided according to their origin, portal of entry, or the character of the lesions that they produced.

From their source they may be recognized as of *animal*, *vegetable*, or *mineral* origin; with the first of these would be grouped the venom of serpents, the poisons of bees, biting insects, cantharidin, etc. Belonging to the second group are opium, strychnin, atropin, and other well-known remedies derived from the vegetable kingdom. The poisons of mineral origin include arsenic, copper, phosphorus, mercury, lead zinc, etc.

Most of the poisons belonging to these groups enter by the alimentary canal, a few may be introduced by cutaneous absorption; some enter with the inspired air. Entrance by way of the genito-urinary system is rare.

According to their mode of action it is possible to recognize *corrosive poisons*, which, in contact with the tissues, at once manifest a destructive tendency. *Irritant poisons* cause inflammation without actually destroying the tissues which they irritate. Other toxic agents—called by the toxicologists *neurotic poisons*—usually give rise to no structural alteration at the point of absorption, but on entering the economy manifest their influence through the brain (cerebral poisons) or spinal cord (spinal poisons), or both (cerebrospinal poisons); they may or may not affect the organs of circulation (cardiac or cardiovascular poisons). That this classification, commonly accepted by toxicologists, has its limitations is shown by the fact that arsenic acts on the mucosa of the alimentary canal as an intense irritant and after absorption may attack the nerves (arsenical neuritis).

Poisoning may be *acute* or *chronic*, and the same agent may be the cause of either form. In large doses arsenic produces an acute poisoning; small, frequently repeated doses cause chronic arsenical poisoning. Similar types of poisoning are produced by mercury, lead, phosphorus copper, arsenic, etc.[1]

[1] Brouardel, "Les Intoxications (arsenic, phosphore. cuivre et mercure, plomb)," Paris, 1904.

Some poisons entering the system give rise to a succession of phenomena to which the term **intoxication** has been applied. Recognizing that within the alimentary canal poisons are produced the absorption of which causes marked symptoms, Bouchard promulgated the term **autointoxication.** That poisons can be formed in the alimentary canal and that they may be absorbed and exert deleterious influences on the tissues has been fully established. Extended knowledge seems to indicate a number of sources from which such poisons could arise. They might be derived from (1) imperfectly digested food, (2) result from the reabsorption of secretions normally present in the intestine or be produced by the action of the intestinal flora on (3) food or (4) secretion, or (5) on both. A further study of certain forms of disease showed that definite processes might arise from the accumulation in the system of materials that should be excreted. No better example of this is seen than the promptness with which symptoms follow arrest of renal excretion.

When physiologic inquiry, by modern methods, was directed to the ductless glands, and particularly when certain diseases of these structures were closely investigated, it was found that excessive glandular activity might throw into the circulation a quantity of secretion with which the body was unable to cope, thereby giving rise to manifestations due to poisons clearly of endogenous origin and therefore belonging to the autointoxications. Such toxic bodies, produced by cells, belong to the group of substances that Prudden has designated **histogenic poisons.**

Further, it is evidently the function of some organs to destroy, or render inert, certain poisons produced by the tissues and normally circulating in the blood or neutralized at their sources. Such action may be accomplished by the direct influence of gland cells upon substances brought to them or by a secretion manufactured by the gland and poured into the circulation; by the first method the result is attained in the blood; by the second it may be accomplished in the circulation, or the blood carrying the antidote may act upon the poison at the place where the latter is normally produced. It is evident that if the gland in question fail to perform its function those substances which, in one of the ways suggested, it would normally render harmless, may accumulate in the organism in sufficient quantity to manifest toxic properties.[1] Here, then, was another group of poisons arising within the organism itself and causing phenomena that could with propriety be included among the autointoxications. If the term had not already lost its specific value, its use under the new conditions led to confusion rather than clearness.

In addition to the difficulties already indicated there were still several groups of poisons not provided for by existing classifications. When any tissue within the body dies, the resulting changes which it undergoes during the process of removal are associated with the production of toxic agents; these substances Adami calls **disintegrative endogenous poisons.** If hemorrhage occur in the tissues, disintegration of the blood liberates bodies which, entering the circulation, may exert a toxic action. There is reason to believe that the death of any cell liberates noxious materials for

[1] See Addison's Disease, chapter on Diseases of the Adrenal, also Myxedema, Cretinism, etc., in chapter on Diseases of the Thyroid.

which, in normal quantities, adequate provision is made. When, however, cell or tissue death exceeds certain limits, the mechanism which, during health, converts, renders inert, or excretes the resulting catabolic product is overwhelmed and the accumulated poison manifests its presence by phenomena possessing, in some instances, fairly constant characters. It is the absorption of such dead material that accounts for the aseptic fever following injuries (fracture of bone) with which bacterial influences apparently have nothing to do. Attention has already (p. 71) been called to the evidence of poison production, absorption, and definite action on the viscera when the surface of the body has been injured by heat. The exact nature of all such toxic substances is obscure; we see the results of their action without possessing any accurate knowledge as to their composition, mode of influence, or ultimate fate.

There are still two groups of poisons produced in the body and differing in their mode of production from any of the foregoing; these are the **parasitic poisons,** which may further be subdivided into those due to or arising from (*a*) animal, (*b*) vegetable parasites present in the host. The parasitic poisons will be more specifically considered with diseases caused by bacteria and animal parasites.

The foregoing attempt to show how complex has become the problem of the proper classification of poisons indicates, in part at least, the difficulty in formulating a systematic presentation of the subject. Of the various classifications that have been offered, the writer is unfamiliar with any that is superior to that suggested by Adami.[1] It covers the essential groups to which reference has already been made and I take the liberty of quoting it in full:

(1) EXOGENOUS.

Due to the actions of poisons entering the system from without.

i. **Exotic** or introduced; due to the action of substances foreign to the organism, which gain entrance through the skin, the digestive, the respiratory or the genito-urinary tract.

ii. **Indigenous** or excretory.
   - (*a*) *Indirect autointoxication*, due to the absorption of retained excreta.
   - (*b*) *Disintegrative*, due to the absorption of decomposition and fermentation products developed in the external secretions through the action of those secretions.

(2) ENDOGENOUS.

i. **Direct autointoxication.**
   - (*a*) *Internal secretory*, due to the action of excessive or unneutralized or modified discharges from the cells of one or other tissue acting directly upon the other tissues of the body without previous discharge from the system.
   - (*b*) *Disintegrative*, due to the action of the products of decomposition and necrosis of one or other tissues acting in a similar manner.

ii. **Parasitic.**
   - (*a*) *Microparasitic*, the infections.
   - (*b*) *Macroparasitic*, poisons from animal parasites.

It has been shown with regard to many poisons that the action is essentially chemical, and this is probably true of all. By disturbing

[1] "American Medicine," July 27, 1901, p. 131.

the normal chemistry the function is necessarily perverted or arrested and the structure sooner or later yields to the abnormal influence. The recognition that the action of a given poison is almost certainly a chemic problem at once offers an explanation for phenomena otherwise most obscure. A poison exerts its influence by combining with the first suitable substance with which it comes in contact. This **elective action of poisons** is shown by the combination of silver salts with albumens and by the local action of a number of poisons which destroy tissue at the point of contact and are themselves at the same time rendered inert. Other poisons pass beyond the external barriers upon which, in some instances, they exert no injurious influence. Carbonmonoxid manifests no irritative action on the respiratory passages, but, entering the blood, combines with the hemoglobin so intimately that the latter loses its power to carry on the normal oxygen and carbondioxid exchange. In chronic arsenical poisoning the metal shows a special affinity for keratin, and may be demonstrated in the hair, nails, and in the nervous system (neuro-keratin). The tendency of lead to attack the peripheral nerves (lead neuritis) rests upon a similar chemic basis. Although conclusive evidence is wanting, there seems no reason to doubt that the therapeutic action of many drugs can be satisfactorily accounted for in no other way; the influence of cerebral sedatives and the action of such medicaments as strychnin are most easily explained by the assumption that they effect a more or less temporary combination with certain cells of the central nervous system. The modern view of acquired immunity[1] is based on the conviction that certain bacterial toxins combine with cells, and it has been shown experimentally that tetanus toxin in an emulsion of tissue from the central nervous system is carried down by the sediment, leaving the supernatant fluid relatively non-toxic; in other tissues or cell suspensions the toxin is not similarly anchored. Toxicologists are familiar with the fact that after various forms of poisoning the toxic agent, postmortem, can be found in largest quantities in certain organs, particularly the liver, brain, spleen, and kidneys. That any poison is more abundant in a given tissue than in the blood clearly establishes that some local influence extracts it from the circulating fluid and anchors it in the new position. There is nothing so very extraordinary in this fact if it be recalled that in the organization of normal bone the developing tissue must possess a higher affinity for lime salts than the other tissues or the blood, which clearly must present to all structures the same general proffer; each elects the substance suited to its particular needs. I do not recall who was responsible for the crystallized truth, that cells are not nourished, they nourish themselves; it is equally true that they are not poisoned, they poison themselves.

The elective affinity of carbonmonoxid for hemoglobin, while arresting the function, does not seem fraught with any immediate danger to the cell. Other substances, however, combine with and promptly destroy the erythrocyte. The process is properly termed **erythrocytolysis,** but brevity and convenience have led to the adoption of the word **hemolysis.** The substance producing the cell change is called an **erythrocytolysin** or **hemolysin.** Potassium chlorate, arseniuretted hy-

[1] See Theories of Immunity, during the discussion of which this subject is again reviewed from a somewhat different aspect.

drogen, toluylenediamin, are hemolytic. The introduction into the circulation of blood derived from an animal of another species is promptly followed by hemolysis, the introduced blood rapidly disappearing and the blood of the animal experimented upon also suffering to a more or less marked degree. That certain bacteria produce hemolysins is now fully established. Among the organisms whose poisons contain hemolytic substances may be mentioned streptococci, certain of the staphylococci, Bacillus pyocyaneus, Bacillus diphtheriæ, Bacillus tetani, and Bacillus typhosus. Certain animal parasites are the source of hemolytic bodies. Red cell destruction is present in a varying degree in practically all forms of malaria, and constitutes one of the most conspicuous features of that type called "blackwater" fever; in this form the destruction of red cells may be so marked that the plasma of the blood is tinged and the blood coloring-matter poured out from the kidney in such quantities that the urine is highly colored, by reason of which fact the condition has received the name hemoglobinuric malaria, or **malaria hæmaturia.** In cattle the intracellular parasite (Piroplasma bigeminum) causing Texas fever is actively hemolytic. At present it seems highly probable that the anemias caused by the Dibothriocephalus latus and the uncinaria result from the action of hemolytic poisons secreted by the parasites. The poisons of snakes contain hemolytic substances.[1] Flexner and Noguchi have also shown that venoms contain a number of cytolysins, and that, aside from the hemolytic poisons, there are substances that attack the parenchymatous cells of a number of organs.

The foregoing review of a small number of the many poisons known to attack the red blood-cell indicates, in a general way, the character of the toxic agents that may attack the somatic cells. It has been possible to demonstrate, for a large number of the body cells, poisons the action of which, if not specific, closely approaches that quality.[2] **Hepatolysins** attack particularly the liver cell, **nephrolysins** the renal parenchyma; Flexner and Noguchi conclude that the hemorrhages seen in rattlesnake poisoning are due to the action of a cytolysin which they call **hemorrhagin,** affecting particularly the endothelium of the blood-capillaries. The field of cell intoxication or destruction is but superficially explored, and this conception of the action of poisons, and an extended information concerning immunity, promise limitless progress in our knowledge of morbid processes. Many so-called neuroses and diseases now regarded as "functional" may be traced to the action of subtle poisons the origin of which we may hope to lay bare. Bell[3] has recently written a most interesting paper on the relation of endogenous poisons to mental disturbances.

[1] See paper by McFarland, "Phila. Med. Jour.," Feb. 15, 1902; Flexner and Noguchi, "Univ. of Penna. Med. Bull.," 1902, xiv, 438; "Jour. of Exper. Med.," 1902, vi, 277; "Univ. of Penna. Med. Bull.," Nov., 1902. Symposium on Serpent Venoms, "Proc. of the Path. Soc. of Phila.," Feb., 1903. Lamb and Hunter, "Lancet," 1904, vol. ii. Flexner and Noguchi, "Jour. of Path. and Bact.," vol. x, p. 111.

[2] The literature of this subject is voluminous and widely distributed; the reader will be able to trace the most important articles and glean essential facts from paper by Pearce, "Journal of Med. Research," 1904, vol. xii, p. 1; also consult Vaughan and Novy, "Cellular Toxins," 4th ed., 1902; Herter, "Chemical Pathology."

[3] "Jour. Amer. Med. Assoc.," Feb. 20, 1904, p. 507.

Before dismissing the poisons as causes of morbid processes it is necessary to note the occurrence, in pregnant women, of a form of endogenous intoxication known by obstetricians as the **toxemia of pregnancy.** During gestation, under conditions at present imperfectly understood, there arises a series of phenomena strongly suggesting the presence of one or more powerful poisons. The exact nature, origin, and ultimate fate of the toxic substance or substances remain obscure. Ewing believes that the metabolic disturbance depends upon deficient oxidizing capacity on the part of the liver, which fails to combine the proteid derivatives to form urea. Among the many manifestations of this peculiar toxemia may be mentioned cutaneous disturbances, ptyalism, the nausea and vomiting of pregnancy, jaundice, albuminuria, fatty degeneration and other disturbances of the liver, and eclampsia independent of or with albuminuria; the symptomatology indicates the presence of some intensely toxic substance, possibly a number of poisons.[1] It is possible that the insanities of pregnancy have a similar origin. In the severer forms of toxemia the liver appears to bear the brunt of the injury, although kidney lesions are present in over ninety per cent. of the cases.

The influence of certain internal secretions in maintaining body nutrition, and the important nutritional disturbances resulting from excess as well as inadequacy, will be discussed when dealing with the special pathology of the particular organs producing these secretions; hyperthyroidism and athyroidism will be discussed with diseases of the thyroid, Addison's disease with the adrenals, etc.

[1]See papers by Davis, "Amer. Jour. of the Med. Sci.," Feb., 1905; Stone, "Amer. Gynecol.," Dec., 1903, p. 518; Ewing, "Amer. Jour. of Obstet.," 1905, vol. li, No. 2.

CHAPTER III.

BACTERIA AS CAUSES OF DISEASE.

GENERAL CONSIDERATIONS.

Near the bottom of the scale of vegetable life may be recognized three groups of microorganisms which, in a general way following Nägeli, may be divided into (1) the Schizomycetes, fission fungi, or bacteria; (2) Blastomycetes, saccharomycetes, yeasts or yeast fungi, or budding fungi; (3) Hyphomycetes, molds, mold fungi, or mucorini, and sometimes called the branching fungi. This classification is open to important objections and must be regarded as provisional; it serves the purpose of labeling, facilitates grouping, and in other ways aids our study of these parasites and the diseases caused by them.[1]

BACTERIA.[2]

Bacteria are microscopic, unicellular organisms of vegetable origin. They vary in size from ultramicroscopic bodies, too small for demonstration by optical appliances at present at our disposal, to larger units the maximum length of which may exceed the diameter of a red blood-cell.[3] From eight to twelve of the medium-sized cocci can be placed in a row across the surface of an erythrocyte. The smallest demonstrable object by the best modern microscopes measures about 0.2 μ; a number of bacteria are more minute.[4]

Structure.—Bacteria consist of a non-chlorophyllous protoplasm, which, in some forms, is condensed at the periphery, giving rise to a layer resembling a cell wall; a few possess outer cellulose membranes and some are encapsulated. Butschli has shown that the plasma of bacteria is a coagulable gelatinous substance which may be expressed from the interior of the cell. He recognized in most bacteria an outer membrane which does not stain and a faintly tingible adjacent zone, while

[1] It is not the purpose of this work to discuss systematically the organisms that cause disease. The student is referred to numerous excellent works on bacteriology, among which may be mentioned Kolle and Wassermann, "Handbuch der Mikroorganismen"; Flügge, "Die Mikroorganismen," 1896 edition; Macé, "Traité de Bacteriologie," 1901, 4th edition, with Atlas; Miquel and Cambier, "Traité de Bacteriologie Pure et Appliquée," 1902; Muir and Ritchie, "Manual of Bacteriology," American edition, edited by Harris; Sternberg, "Text-book of Bacteriology"; McFarland, "Text-book of Pathogenic Bacteria."

[2] In the present edition the chapter on Bacteriologic Technic has been placed near the end of the volume.

[3] The measurement of bacteria is usually made in microns. The term "micron" is an abbreviation for micromillimeter, which is the one-thousandth part of a millimeter; in other words, about the twenty-five thousandth part of an inch. The word "micromillimeter," or "micron," is practically never written out, but is indicated by the Greek letter μ.

[4] For review of the ultramicroscopic bacteria see Roux, "Bulletin de l'Institut Pasteur," 1903, vol. i, Nos. 1 and 2; Hektoen, "Jour. Amer. Med. Assoc.," Aug 15 and 22, 1903.

near the center is an area staining intensely and, though probably not a nucleus, possessing some of the characters of that structure.

Motility.—Many bacteria possess the power of locomotion. Motile cocci, bacilli, and rigid spirals are propelled by the exceedingly rapid vibratory motion of thin, lash-like processes, extending from the side or poles of the organism, called flagella. (For the demonstration of flagella see chapter on Bacteriologic Technic.) Certain of the flexible spirilla possess the power of moving from place to place by (1) a rotatory motion in their long axis, or (2) by an undulatory or snake-like movement.

Reproduction of the schizomycetes is principally by the process of *fission: i. e.*, a cell having reached its full development, simply divides into two or more segments. Reproduction also takes place by *spore formation.* Two kinds of spores have been described: (1) Arthrospores and (2) endospores.

Arthrospore formation is described by de Bary and Hueppe as occurring in cocci. In certain chain cocci there are a few cell elements that acquire those characteristics common to spores without any apparent differentiation of cell protoplasm. They appear larger than the other elements of the chain; their borders are more sharply defined, and the cell-wall appears to be thicker; they possess a much greater resistance than the other cells to all conditions incompatible with life, and their protoplasm is darker or more highly refractile. When these bodies are removed from conditions that brought about the death of the other chain elements, and when placed in favorable soil, they develop the characteristic chains. This type of spore formation is not universally accepted; the bodies thought to be arthrospores have no enveloping membrane, are without characteristic stain reaction, and it is not known that they possess increased resistance to destructive agencies.

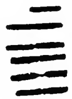


FIG. 51.—PROPAGATION BY FISSION.—(*Coplin and Bevan.*)

Endospore formation is the development within the bacterial cell of spheric or oval bodies possessing unusual resistance to conditions incompatible with the life of the mature organism. Usually the spores make their appearance only when germ plasma manifests degenerative changes and becomes granular. The spore appears at first as a small, bright point, which gradually increases in size until its diameter may exceed that of the parent cell. Frequently the spore develops in the center of the organism, when, if the microbe is a bacillus, it may appear spindle-shaped. If the spore arises at one of the poles of a bacillus, the organism will appear club-shaped or pendulum-like—a characteristic of the Bacillus tetani. Endogenous sporulation is an attribute of bacilli and a few spirilla, although Zopf has described the formation of endospores in certain micrococci, and Escherich in the Sarcina pulmonum. It is generally believed that spore formation should not be regarded as a process of multiplication, but rather as a stage in the perpetuation of the organism. Usually sporulating bacteria do not manifest the tendency except in the presence of conditions unsuited to continued proliferation,—a fact strongly suggesting that the process is directed toward establishing heightened resistance to external agencies. Under favorable conditions, spores always develop

into organisms identical with those from which they were derived.[1]

The processes of reproduction, as seen in yeasts and molds, are described and illustrated with those fungi.

It is impossible to distinguish between the many species of any one kind of organism by morphologic peculiarities alone, therefore the biologic characteristics must be developed to serve as a guide to satisfactory identification. It is well known that several varieties of the micrococcus pyogenes are morphologically identical, and, were it not for certain biologic peculiarities, it would be impossible to differentiate one from another. Those points commonly worked out will be found tabulated in the chapter on Bacteriologic Technic.

Microorganisms forming pigment in the process of growth are known as **chromogenic bacteria,** or **chromogens.** Breyerinck and Schröter divide the chromogenic bacteria into (1) chromoparous, in which the coloring-matter surrounds the colorless organism and is apparently a secretion of the germ; (2) the chromophorous, in which the cell protoplasm is pigmented, and (3) the parachromophorous, those containing colored granules in the cell wall.

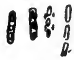


FIG. 52.—FROM CULTURE OF BACILLUS MEGATERIUM.
Showing development of spores within the capsules or bacillary envelop, which, later, breaks up and liberates the spores. On the extreme right are shown three bacilli developing from the spores.—(*Coblin and Bevan.*) × 800 diameters.

Zymogenes, or **zymogenic bacteria,** are those capable of inducing fermentation.

Saprophytic bacteria are those incapable of producing disease. Such organisms subsist on dead animal or vegetable matter and may be present in a gangrenous limb or blood-clot in the uterus, but are not able to invade the living tissues. While this distinction between saprophytism and parasitism may sometimes hold, it cannot be applied too strictly. Theobald Smith[2] suggests that many pathogenic bacteria may at some time have been saprophytic.

Pathogenesis.—Pathogenic bacteria are the disease-producing organisms. Koch has formulated, as conclusive evidence of the specificity of a given organism, the following requirements, which must be met:

1. *The organism must be present in all cases of the disease.*
2. *It must be grown in pure culture.*
3. *It must produce the disease by inoculation in susceptible animals.*
4. *From such animals the germ must be obtained and again cultivated in pure culture.*

To this cycle of proof has recently been added another demand for experimental evidence of pathogenicity.

5. From cultures of the organism there should be demonstrated a toxin that, without the germ, will produce the phenomena of the disease, or by means of which an antitoxin or immunizing substance can be developed in susceptible animals, lessening or removing their liability to the disease presumed to be produced by the organism in question.

Any evidence less conclusive than that afforded by the foregoing requirements may be considered as presumptive knowledge of specificity. So many diseases occur in man and not in lower animals that the best we can hope to do in such cases is to produce, by experiment or otherwise,

[1] For recent paper on sporulation in anthrax and other spore-bearing bacteria see Selter, "Centralbl. f. Bakt.," Oct. 17, 1904, p. 186.
[2] "Jour. of the Boston Soc. of Med. Sci.," 1900, vol. iv, p. 95.

as much of the proof as possible, and to accept the germ as the cause in the absence of any equally or more rational explanation. In some diseases—for example, leprosy—this is practically the stage at which the scientific inquiry at present rests. It is also most important to recognize that the disease-producing power of well-known pathogenic organisms is by no means always the same. Some bacteria under cultivation entirely lose their ability to produce disease even in susceptible animals. Saprophytic bacteria under unusual conditions may occasionally become pathogenic, and it is highly probable that some pathogenic forms have acquired this faculty.

Toxicogenic Bacteria.—Certain bacteria are endowed with the property of elaborating poisonous bodies without themselves being able to exist in the living tissues. As will be pointed out later, all disease-producing bacteria are toxicogenic to a certain degree.

Liquefaction.—Those bacteria that in their growth liquefy Koch's flesh-peptone-gelatin are known as liquefying. They probably elaborate a ferment having this property. The exact ferment to which this liquefaction is due is a member of the proteolytic enzymes. Organisms not having this property are known as the nonliquefying bacteria.

The power of **producing gas** is marked in some forms of bacteria and is absent in others. Gas production is a conspicuous feature of certain anaerobic organisms, among which may be mentioned the bacillus of tetanus and some of the bacteria giving rise to gaseous abscesses and gangrene. A number of the intestinal bacteria produce gas, and the usefulness of yeasts in the arts depends, to a large degree, upon this quality. Of the numerous gases produced by the growth of bacteria, carbonic acid is the most common.

Some bacteria **coagulate milk,** and this may be used as a test in studying species.

Stain Reaction.—Many bacteria possess more or less constant stain reactions, and a few microorganisms are identified, in part at least, by their taking certain dyes or staining by certain methods. The special methods are given with each organism, but the following list of bacteria, with their reactions to Gram's method, is introduced for convenient reference:[1]

Stained by Gram's Method.	*Not stained by Gram's Method.*
Bacillus diphtheriæ.	Bacillus typhosus (and group).
Bacillus pseudodiphtheriæ.	Bacillus coli (and group).
Bacillus anthracis.	Bacillus anthracis symptomatici.
Bacillus tetani.	Bacillus mallei.
Bacillus lepræ.	Bacillus ulceris mollis.
Bacillus aerogenes capsulatus.	Bacillus dysenteriæ (and group).
Bacillus tuberculosis.	Proteus vulgaris. (Group.)
Bacillus xerosis.	Bacillus œdematis maligni.
Actinomyces.	Bacillus influenzæ.
Pneumococcus.	Diplococcus intracellularis meningitidis.[2]
Streptococci.	Pneumobacillus (Friedländer).
Staphylococcus pyogenes aureus.	Gonococcus.
Staphylococcus pyogenes albus.	Spirillum choleræ Asiaticæ (and group).
Staphylococcus pyogenes citreus.	Bacillus pestis.
Micrococcus tetragenus.	Bacillus icteroides.
Bacillus pyocyaneus.	

[1] For method see chapter on Bacteriologic Technic.

[2] Recent studies of the meningococcus show that the reaction of this organism to Gram's method cannot always be depended upon for differentiating it from the pneumococcus.

Thermal Death-point.—Each organism has what is known as its optimum temperature, at which the growth is most luxuriant and above or below which it becomes less and less free as the change progresses. Eventually, temperatures are reached so high or so low that growth is arrested. Cold does not kill, but a sufficiently high temperature destroys any germ. The exact temperature proving destructive to viability is known as the *thermal death-point*. As moist heat and dry heat are not equally efficacious, each will have its own thermal death-point. Cultures in different media and of different ages often show marked differences in the temperature necessary to kill.[1]

Aerobic and **anaerobic**[2] are terms introduced by Pasteur to denote that an organism requires the presence or absence of oxygen as an essential to its growth. It was proposed at one time to classify bacteria upon this basis, dividing them into two groups,—aerobic and anaerobic,—but it was soon discovered that certain organisms might be cultivated either in the presence or absence of air, though such bacteria usually showed a preference for one or the other condition. This led to the introduction of the terms facultative and obligate. An *obligate organism* requires absolutely one or the other condition. A *facultative organism*, while showing a marked preference for one condition, may develop under the other. Although the hope of thus classifying bacteria has been abandoned, the terms are retained, and are now used for the purpose of description as well as aids to identification.

Photogenesis.—Many bacteria are endowed with the power of producing phosphorescence.

The faculties of producing color, fermentation, disease, etc., are simply properties, and one or all may be possessed by a single organism. Furthermore, an organism, under varying conditions, may be chromogenic or nonchromogenic, zymogenic or nonzymogenic, aerobic or anaerobic, pathogenic or nonpathogenic. Again, a bacterium that is pathogenic for one animal may be wholly destitute of this property when injected into an animal of another species.

Other Bacterial Products.[3]—In the process of proliferation and growth bacteria abstract from the surrounding media certain bodies that enter into and become a part of the chemistry of the organism. After subserving a useful purpose in the economy of the cell and undergoing important changes, many of these bodies are liberated. Not only are certain bodies elaborated within the cell, but, as a result of abstracting certain elements from the surrounding medium, the chemistry of the nutrient is changed. If the elements taken up by the germ and utilized as food are thrown off by the cell, and again enter the surrounding medium, they no longer possess the same chemic affinities, and hence do not form again the same molecular combinations. As these products are to a certain extent dependent upon the character of the nutrient, it can be understood that the growth of a given germ upon different media may to some degree modify its products. Different bacteria growing upon the same medium elaborate substances dissim-

[1] For method see chapter on Bacteriologic Technic.
[2] For methods of demonstration see chapter on Bacteriologic Technic.
[3] For an exhaustive review of bacterial products see Vaughan and Novy, "Cellular Toxins," 4th edition, 1902; also Oppenheimer, "Toxine und Antitoxine," Jena, 1904.

ilar, chemically and physiologically, and the same organism on different media may yield other products. The bacillus typhosus in meat infusions produces a poisonous alkaloid, in peptone solutions it does not. Within certain rather wide limits each organism produces one or more bodies as characteristic of its growth as the alkaloids of certain vegetable forms of a higher type. Of the ultimate chemistry of many bacterial products little is known; we deal more with the results of their activity than with the bodies themselves.

Among the important products of bacterial life are soluble ferments, or **enzymes.**[1] These are thrown off from the cell, and, entering the surrounding medium, induce chemic changes, which are probably directed toward a kind of predigestion, which enables the growing germ to obtain nourishment that previously was not in an assimilable form. Certain of these ferments split up starch in a manner resembling diastase, and hence they are called *diastatic* or *amylolytic ferments*, in their action resembling the ferments normally present in the saliva and pancreatic secretion.

Other enzymes break up the proteids, converting albumin into albumose and into peptone, and hence they are called *peptonizing* or *proteolytic ferments*. Others break up fat (lipolytic ferments), and some possess the property of converting cane-sugar into glucose by a process of inversion, while other ferments lead to precipitation of the casein in milk, which may again undergo resolution in the presence of other members of the group. Through the activity of certain of these enzymes fermentation, the oxidation of carbohydrates, etc., occur, leading to the formation of alcohols, organic acids, etc.[2]

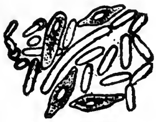


Fig. 53.—Bacillus butyricus. × 1000.

Fig. 54.—Bacillus acidi lactici. × 800.

Various **acids**[3] are produced by the specific action of bacteria. Among the most important are *lactic*, *acetic*, and *butyric* acids. The *Bacillus acidi lactici* produces lactic acid from milk-sugar, and is considered the usual cause of acid fermentation in milk.

The mycoderma aceti (Bacillus aceticus) in the presence of oxygen produces acetic acid in dilute solutions of alcohol. Butyric acid is produced by a large number of bacteria; the most important one, however, is the Bacillus butyricus, an anaerobic organism.

The **alkali**[4] most commonly elaborated by bacteria is ammonia, which is a final product of proteid dissolution: *e. g.*, bacterial disruption of urea, leading to the formation of ammonia and carbon dioxid.

Putrefaction of animal and vegetable bodies is brought about by a great variety of bacteria. The products of this process are numerous, and are usually divided into two classes—the volatile and the nonvolatile.

[1] For interesting paper on the possible production of disease by enzymes independent of any organism, see Moore, "Jour. of State Medicine," April, 1904.

[2] For review of previous work and original observations on enzymes, see Buxton, "Amer. Med.," July 25, 1903, p. 137.

[3] See Petruschky, "Centralbl. f. Bakt.," Bd. vi; 1890, Bd. vii; 1896, Bd. xix. For method of testing reaction see chapter on Bacteriologic Technic.

[4] See Petruschky, "Centralbl. f. Bakt.," 1889, Bd. vi; 1890, Bd. vii; 1896, Bd. xix. For method of testing reaction see chapter on Bacteriologic Technic.

The malodorous gases belonging to the former group are commonly the product of anaerobic bacteria. Novy has very properly considered putrefaction to be a putrid fermentation, differing from other fermentative processes in the fact that the bacteria are dealing, in the change under consideration, with proteid matter, and only to a limited degree with sugars and starches.

Ptomains are basic substances containing nitrogen, and resemble in chemic constitution such vegetable alkaloids as morphin and strychnin. Like the vegetable alkaloids, in combination with acids, they form definite salts. It was at one time believed that bacteria owed their disease-producing power to the ptomains. This is now known not to be the case, as a number of intensely pathogenic bacteria—for example, the diphtheria bacillus—do not elaborate ptomains.

The most important bacterial products, so far as at present known, are the **toxins.** Toxins, as elaborated by the pathogenic bacteria, resemble to a varying extent the albuminoid poisons, abrin and ricin, and the venom of serpents. While this resemblance is possessed to a varying degree by all, each toxin is the specific product of a given microorganism. Investigators are agreed that the toxins are not basic bodies like ptomains; in some respects they resemble globulins, but their proteid nature is not proved; Roux and Yersin thought they might be enzymes. As a matter of fact, we have probably never seen a pure toxin, know next to nothing of their ultimate composition, are unfamiliar with the chemic changes which evolve them, and are but indifferently acquainted with their action in the production of disease.

Toxins are unstable compounds, some being destroyed by comparatively low temperatures (60° to 80° C.), and, in most instances, exposure to sunlight destroys or materially alters them. They are the most active poisons known: it is estimated that $\frac{1}{275}$ of a grain of the pure toxin of tetanus would be fatal to an adult. They are for the most part destroyed by the digestive juices of the body, and hence are innocuous when administered by the stomach. Entering the circulation, they manifest their poisonous properties upon many of the cells of the body, each toxin apparently selecting certain cellular elements, which are said to show an unusual degree of susceptibility. It is not improbable that the poison directly combines with, or is taken up by, the cells, as already mentioned of tetanus. (See p. 78.)

Some toxins are diffused from the bacteria into the culture media in which they are found in the largest quantities and in the purest state; these are called **extracellular toxins**; conspicuous among the organisms producing this type of toxin are the diphtheria bacillus and the bacillus of tetanus. Another group of toxins are not discharged into the culture medium by the growing germ, but are retained in the bacterial cell. These are called **intracellular toxins**; the chief poisons produced by the typhoid bacillus, colon bacillus, the Bacillus enteritidis of Gärtner, the dysentery bacillus, spirillum of cholera, and a few other pathogenic organisms, are almost exclusively intracellular; filtered cultures of such organisms are but feebly toxic, and any poison that they contain could easily have been derived from the protoplasm of dead germs commonly present in such cultures as the result of bacteriolytic processes. The destruction of such organisms in the tissues is fraught with danger to the economy on account of the poisons liberated by the disintegration

of the dead bacterium. In this connection it is interesting to note that a number of nonpathogenic organisms contain highly toxic intracellular poisons, and, therefore, if introduced into living tissues in sufficient quantity and destroyed by the bacteriolytic juices and cells they may liberate sufficient poison to cause definite tissue alterations; Vaughan has proposed for this type of organism the name **toxicogenic bacteria,** which would include also nonpathogenic organisms the poisons of which are extracellular. In the case of bacteria containing intracellular poisons it is evident that the greater the bacteriolysis, the larger the amount of poison liberated in the body, and it is not improbable that in some instances—for example, croupous pneumonia—the so-called crisis depends upon the rapid destruction of bacteria and coincident liberation of intracellular poisons in large quantities. Auclair[1] states that the intracellular poisons are usually more resistant to heat and very much less diffusible in the tissues than the extracellular toxins. In common with a number of observers, Auclair has shown that in the case of some organisms these intracellular poisons are extremely complex, and that by the use of different solvents toxic substances having dissimilar properties may be extracted from the bacterial cell; the name etherobacilline, xylolbacilline, chloroformbacilline, etc., has been given to such extracts derived from the tubercle bacillus. For the intracellular poisons of bacteria the name **endotoxin** has been proposed. As will be seen later, when discussing the question of immunity, the extracellular poisons are antagonized in the tissues by substances called antitoxins, and the intracellular poisons by the bacteriolytic protective agents.

There is still a third group of bacteria in which the elaborated poisons are both intracellular and extracellular, although the facts at present at our disposal indicate that even in these organisms the diffusible toxic substances are unlike the more firmly anchored intracellular toxins. The filtrate from the unheated cultures of the tubercle bacillus contains definite poisons; if the culture is boiled before filtration, the toxicity of the fluid is increased, indicating that some of the intracellular poisons are extracted by the hot fluid; the bacilli, however, still contain a quantity of undissolved poison, as can readily be shown by further extracting them with a number of solvents and administering to animals the substance so obtained.

That bacteria produce disease almost exclusively through the activity of their toxins is now generally admitted. In some instances the toxin exerts most of its influence directly at its point of production. According to Auclair, the toxins of the actinomyces, gonococcus, and tubercle bacillus act locally; the typhoid bacillus, streptococcus, and staphylococcus poisons manifest both local and general action. It is well known that the tetanus toxin exerts no important local influence, but manifests its poisonous quality almost, if not quite, exclusively by way of the nervous system. The poisons produced by the diphtheria bacillus are responsible for some of the important local changes, but the intense systemic action of the toxin is indicated by the wide-spread lesions of diphtheria, such as destruction of cells in the liver, degeneration of nerves, changes in the myocardium, irritation and inflammation of the kidney, etc.;

[1] "Arch. de Méd. Exper. et Anat. Path.," Nov., 1903, p. 725.

Welch[1] and Flexner have demonstrated that, in addition to its soluble toxin, the diphtheria bacillus possesses an intracellular poison concerned in the production of false membrane. The increase in the leukocytes seen in a number of infections is clearly attributable to the action of the toxins on leukocyte-forming tissues. That such structures are influenced in infection is shown most clearly by the studies of Muir[2] and Longcope.[3] Burton-Sanderson[4] has crystallized our previous knowledge of toxin, particularly calling attention to the fact that while it is necessary to recognize the deleterious influence of bacterial poison, it is equally important to appreciate that almost exclusively through this influence the tissues of the body are stimulated to the production of antagonizing agents (antibodies, see Immunity), through the intervention of which bacterial action is arrested.

The ultimate fate of bacterial poisons is not known; when neutralized or destroyed by the body-cells or fluids, or in any way rendered harmless, they may be excreted by the emunctories.

Subinfection.—As already stated when considering poisons, it is a well-known fact that small, frequently repeated doses of such toxic agents as lead, arsenic, mercury, etc., give rise to special forms of chronic intoxication characterized in each instance by a fairly definite clinical picture and more or less constant lesions. A number of observers[5] have conceived the idea that in one way or another small quantities of bacterial toxins, constantly entering, or continuously produced in the system, may give rise to slowly progressing lesions without at any time the manifestations of frank infection. For this condition Adami suggested the name subinfection. It is not impossible that profound anemias and marked structural alterations in organs may in this way be brought about.[6]

The growth of one germ may develop conditions favorable for the pullulation or pathogenic action of another,—a condition called **symbiosis.** The presence of oxygen-absorbing bacteria may assist in securing the necessary anaerobic medium for the bacillus of tetanus, and alcohol-splitting organisms may keep that substance sufficiently low to permit continuous growth of any associated yeasts. It is certain that in the presence of pathogenic organisms which destroy tissue, opportunity for the growth of saprophytic bacteria is afforded and the clinical and pathologic features of infection intensified. It is not established, however, that the organisms of decomposition in any material way facilitate the action of the disease-producing germs. Recent studies in the proliferation of unicellular animal parasites indicate that at least some

[1] "Brit. Med. Jour.," Oct. 11, 1902, 1105; "Lancet," Oct. 11, 1902, p. 977; "Medical News," Oct. 18, 1902, p. 721; "Science," Nov. 21 and 28, 1902; "Postgraduate," Dec., 1902, p. 1416; "Huxley Lecture."

[2] "Trans. Path. Soc. of London," 1902, vol. 53, p. 379.

[3] "Bulletin of the Ayer Clinical Laboratory of the Penna. Hospital," No. 2, Jan., 1905.

[4] "Lancet," November 1, 1902; "Trans. Path. Soc. of London," 1903, vol. 54, p. 1.

[5] This matter has been particularly investigated by Adami and his students; Charlton ("Jour. of Medical Research," vol. viii, p. 344, November, 1902) records some interesting experiments upon the production of anemia by repeated administration of sublethal doses of the colon bacillus and gives bibliography which will start the inquirer on the track of previous literature.

[6] The local action of bacteria is discussed with each organism; see Suppuration, Tuberculosis, Diphtheria, Actinomycosis, etc.

of them require the presence of a vegetable organism through the energy of which food for the protozoon is made available.

Pure or **simple infections** are probably less common than **mixed** or **concurrent infections.** The latter may, by adding one toxin to another, further embarrass tissue resistance and intensify systemic poisoning; this is notably the case in many conditions. Whatever may be the cause of scarlet fever, its lesions are greatly intensified by the coincident streptococcus infection of the throat; the same is true of the influence exerted by the pus-producing organisms in the pocks of variola. When pyogenic bacteria invade tuberculous tissue, local disintegration and systemic intoxication are both increased. On the other hand, facts are not wanting to show that one germ may antagonize the action of another; the virulence of anthrax bacilli is modified in cultures containing the bacillus pyocyaneus.

PATHS OF INFECTION.

Bacteria enter the tissues in a number of ways. The fact that many organisms capable of producing disease are constantly present on the surface of the body, within the alimentary canal and elsewhere, establishes that the various surfaces, both external and internal, constitute protective barriers the efficiency of which necessarily varies. The following are the principal paths through which infections occur:

Transplacental infection has been shown to be possible in anthrax, pneumonia, typhoid, pyogenic infections in which the germs are present in the maternal circulation, recurrent fever, smallpox, glanders, tuberculosis, and syphilis. Wassermann[1] has collected 12 cases in which tubercle bacilli traversed the placenta. There are numerous recorded instances in which anthrax, both natural and experimental, has passed from mother to fetus. Konradi[2] concludes that it is possible for the virus of rabies to traverse the placenta. Infection across the placenta is possible only when the organism is present in the maternal blood. It is probable, although not demonstrated in all instances, that the placenta itself must be affected in order to permit infectious material to enter the fetal circulation. It is well known that antibodies in the maternal blood may reach the fetus; it is not established, however, that bacteria may pass from the mother to the fetus without structural changes in the placenta. Syphilis is the only disease in which we have reason to believe that the fetus may deleteriously influence the maternal tissues, themselves previously sound; even here the possibility is not universally admitted. That the syphilitic fetus exerts some action on the maternal organs is indicated by the fact that it may nurse from the mother without danger of infecting her, but can infect a wet-nurse.

Infection through the skin[3] rarely occurs provided the epithelium is intact. Cutaneous and subcutaneous abscesses have been produced by rubbing pus-producing cocci into the skin; the experiment, however, is not always successful, and the fact that these organisms are constantly present on the surface of the body without producing suppurative

[1] "Handbuch der Mikroorganismen," Bd. i, p. 395.
[2] "Centralbl. f. Bakt.," Jan. 25, 1905, p. 60.
[3] For article on the defensive powers of the normal skin see paper by Sabouraud, "Bull de l'Inst. Pasteur," 1904, vol. ii, p. 233.

lesions shows conclusively epithelial protection. In a number of instances I have observed in myself and in my assistants suppurative lesions clearly beginning in the hair follicles of the forearm, and it is not improbable that the appendages of the skin (hair follicles, sebaceous and sweat ducts) afford points for the deposit of bacteria, which, under favorable circumstances, may penetrate the tissues. Many facts go to show that skin of different parts of the body possesses different degrees of protection; the more highly keratinized layers of the palms of the hands and soles of the feet must necessarily be difficult to penetrate. Ordinarily transcutaneous infection occurs through wounds or abrasions which may be microscopic and need not penetrate the corium. The diphtheria bacillus, the streptococcus of erysipelas, and even the tubercle bacillus have been known to infect blistered surfaces.

Infection through the alimentary canal undoubtedly represents the most frequent method by which bacteria enter the body, but even by this route the surface protection in certain parts is relatively high; the thick epithelial layers upon the buccal mucosa, tongue, and esophagus offer much greater protection than the more thinly clad intestine. The latter structure is afforded a certain amount of protection by the bactericidal activity of the gastric juice; it has repeatedly been shown that gastric secretion is destructive to cholera organisms, and that during epidemics of cholera gastric indigestion favors the occurrence of infection. Abrasions about the **mouth,** particularly of the lips and along the gingival margin, may permit the ingress of pathogenic bacteria. It is possible for infection to occur through carious teeth. **Tonsillar infection** has, within recent years, been shown to be of frequent occurrence. Jonathan Wright [1] holds that the tonsillar crypts are test tubes in which bacterial cultures are constantly opposed by the resisting power of the tissues. Lacunar and ragged tonsils, and tonsils with plugged crypts, are particularly favorable for the entrance of bacteria. Streptococci, staphylococci, and tubercle bacilli have been demonstrated in the tonsillar tissue, the last without the histologic changes of tuberculosis. It is generally conceded that tuberculosis of the cervical lymph-nodes is usually due to infection through the tonsils. The depressions and crypts in these organs afford points in which bacteria may secure a certain degree of protection; after recovery from diphtheria (tonsillar and pharyngeal) the bacillus sometimes remains for weeks on the roughened surfaces of the tonsils. The pharynx as a point for bacterial entrance occupies a position of less importance than the tonsils. Infection through the esophageal mucosa is very rare. It has been demonstrated by a number of observers that bacteria can pass through an intestinal mucosa which, so far as can be determined, is intact. Ford,[2] Morgan,[3] Nicholls,[4] and Wrzosek [5] have shown that bacteria are not infrequently present in normal tissues, and Nicholls' studies of the mesentery indicate that germs may enter through the intestine. Typhoid infection is practically always by this route. Cholera organisms proliferate in the cavity of the intestine and from

[1] "Medical News," March 4, 1905, p. 385.
[2] "Jour. of Hygiene," 1901, vol. i, p. 277.
[3] "Lancet," July 2, 1904, p. 21.
[4] "Jour. of Med. Research," May, 1904, p. 445.
[5] "Virchow's Arch.," Bd. 178, p. 82.

this point disseminate their toxic influences throughout the system without giving rise to any characteristic local lesion. Bacteria from the intestine may infect the biliary and pancreatic canals by continuity, or, passing through the intestinal wall, may reach the portal circulation, lymph-glands of the mesentery, or, by way of the chyle vessels and thoracic duct, indirectly enter the circulation. It is generally conceded that, in practically all cases, infections of the appendix are from the intestine.

Infection through the air-passages. The normal mucosa of the nose and its accessory sinuses usually destroys the bacteria coming in contact with it. Once infected, however, extension may occur to sinuses, middle ear, and even the brain. The meningococcus has been demonstrated in the nasal mucosa before and during an attack of meningitis, and Maragliano[1] has produced the disease by spraying the nose of rabbits with cultures of the organism. Bacteria may infect the bronchial mucosa or, passing through this structure, may reach the peribronchial lymphatics and adjacent glands. In a similar way the pulmonary parenchyma and pleura may become infected. Recent studies tend to minimize the frequency with which pulmonary tuberculosis is due to inhalation and direct infection of the lung tissue; by contact with the mucosa of the upper air-passages and bronchial tubes the bacterial content of the air reaching the alveoli is reduced to a minimum.

Infection through the genitourinary system. In certain diseases (gonorrhea) infection of the meatus and the urethra constitutes the ordinary path of entrance. In the male, infection may traverse the seminal tract and reach the testes, from which, or from some intermediate point, the blood may be invaded. In the female urethral infection and consequent cystitis are less constant, but when the bladder in either sex becomes involved an ascending infection may traverse the ureters and renal pelvis, finally attacking the kidney. In the female the **birth canal** offers a particularly favorable field for the growth of bacteria, and when subjected to trauma or in other ways injured may constitute an important center from which dissemination may occur. Gonorrhea in the female attacks the vulva, vulvovaginal glands, vagina, cervix, endometrium, and Fallopian tubes; occasionally infection may extend to the peritoneum, and, from any of the points named, the gonococcus occasionally enters the circulation. In the injuries incident to child-birth abrasions and lacerations in the birth canal open the submucosa through which both local and general infections may occur.

Infection through the conjunctiva. Transconjunctival infection is undoubtedly rare, but well authenticated observations show that the gonococcus, meningococcus, plague bacillus, the ordinary pyococci and the Bacillus influenzæ may enter through this atrium.

PATHS OF EXTENSION.

Once infection has reached the connective tissues by any of the routes indicated it may be restricted to a local lesion, may be propagated by **continuity** or by **contiguity** to adjacent structures, may extend or be carried by the **lymph-stream** or invade the **lymphatics** as a continuous infection, or, reaching the circulation by any path, the organism may

[1] "Gaz. Osped. et Clin.," 1905, No. 19.

be carried and distributed with the **blood.** With regard to lymphatic extension particular attention should be called to the influence of lymph-nodes in limiting the spread of bacteria. Histologically these structures possess an architecture eminently adapted to the filtering function which they clearly manifest. Any infection having a tendency to extend by the lymph paths is commonly shown by enlargement of the nodes through which the lymph of the area drains; thus in syphilis, gonorrhea, chancroid, and other infections of the genitalia the inguinal nodes enlarge. The point of infection in bubonic plague may be shown by the first set of nodes infected, infections of the intestine cause enlargement of the mesenteric nodes, and infections through the mouth and pharynx commonly give rise to swelling in the anterior cervical nodes. The lymph has been shown to possess certain antitoxic and bactericidal [1] qualities, and the fact that tuberculosis may be restricted to a certain node or group of nodes clearly indicates the inhibiting influence which these structures exert.[2]

By whatever route the microorganism enters the tissues, it is met by inhibiting influences with which it must contend for supremacy. The external barriers are of value, but clearly of inferior importance when compared with powerful antibacterial properties possessed by the body-fluids and somatic cells. A proper estimate of these qualities is of the highest interest, and this leads to a consideration of the forms of immunity.

[1] Meltzer and Norris, "Jour. of Exp. Med.," vol. ii, No. 6.
[2] Manfredi, "Virchow Arch.," 1899, Bd. clv, p. 335.

CHAPTER IV.

BACTERIA AS CAUSES OF DISEASE.—(Continued.)

IMMUNITY.[1]

It has long been a recognized fact that a person having suffered from an attack of certain infectious diseases is more or less refractory to subsequent infection by the specific organism of that disease. This insusceptibility differs in different affections and is not the same in all persons. Some of the eruptive diseases, of which but one attack is ever expected, may occur in the same individual more than once; Mycelius[2] has collected 514 cases of smallpox, 33 of scarlet fever, 37 of measles, and 208 of typhoid in which the patients had from two to four attacks.

A number of **forms of immunity** are now recognized. In the first place, it is to be remembered that an absolute immunity to infection rarely, if ever, exists. As a rule, the highest attainable immunity may be broken down, and an animal naturally possessing extraordinary resistance to some particular form of infection may be made susceptible. Thus, the chicken, which is naturally immune to anthrax, may be made susceptible by more or less prolonged immersion in cold water. In a similar way susceptibility may be increased by starvation, improper food, fatigue, shock, hemorrhage, and associated or concurrent infections. The influence of the last-named condition in breaking down a more or less natural barrier to infection is shown by the rapidity with which individuals occasionally succumb to tuberculosis of the lungs consecutive to other infectious processes in those organs. The catarrhal pneumonia incident to measles and influenza may afford a suitable nidus for the lodgment of the tubercle bacillus; the inflammatory changes induced by the presence of foreign bodies in the lung may act as an etiologic factor in the induction of septic pneumonia. The influence of dose on the occurrence of infection further illustrates the relationship between an absolute resistance and an im-

[1] The literature of immunity is widely distributed, particularly in German, French, Italian, and English publications. Aschoff, "Seitenkettentheorie u. ihre Anwendung auf die Kunstlichen Immunisierungsprozesse," 1902; extensive bibliography. Ritchie, "Jour. of Hygiene," vol. i, 1902, pp. 215, 251, 452, with references to 106 articles. Rosenau, "Hygienic Laboratory Bulletin No. 21," 1905, full bibliography. Welch, "Brit. Med. Jour.," Oct. 11, 1902, Huxley Lecture on Recent Studies on Immunity. Ernst, "Theories of Bacterial Immunity," 1903. Discussion on Immunity, Brit. Med. Assoc., 1904, published in "Brit. Med. Jour.," Sept. 10, 1904, p. 557; Bulloch's discussion gives references to 107 articles. Recent summary of Ehrlich's studies will be found in the "Gesammelte Arbeiten zur Immunitätsforschung," 1904. A good review of the subject is now being published in the "Jour. Amer. Med. Assoc.," having begun in the number for January 28, 1905, but not as yet completed. An excellent summary will be found in Bolduan's translation of Wassermann's monograph on "Immune Sera, Hæmolysins, Cytotoxins and Precipitins," 1904. See also Nuttall, "Blood Immunity and Blood Relationship," 1904.

[2] Quoted by McCaskey, "Amer. Jour. of the Med. Sci.," July, 1902.

munity of moderate degree. Buxton[1] has shown that 1 ccm. of fresh normal rabbit's serum may be expected to kill 1,000,000 typhoid bacilli, 50,000,000 paratyphoid organisms, and 100,000,000 cholera spirilla. Large doses bring about fatal results, while smaller doses, even when repeated, may only strengthen the resistance of the animal. The facts adduced go to show that there is first an immunity that approaches an absolute resistance to the disease, and, second, there is a high degree of susceptibility, which may be so marked that the smallest possible dose of an infectious agent will prove fatal to the animal in question. Between these two extremes all possible intermediate forms of reaction to infection may exist. An attempt has been made to subdivide these intermediate gradations of immunity and susceptibility into an absolute immunity and a partial immunity. Such a division is not, in the present state of our knowledge, possible.

Natural immunity is the resistance to some particular form of infection transmitted from parent to offspring. This form of immunity may belong to some particular species in the animal kingdom or to but one race of animals. As examples of this condition may be noted the susceptibility of the field mouse and the immunity of the white mouse to glanders; the relative immunity of the negro to yellow fever and malaria and the great susceptibility of the white race.

When an animal naturally susceptible to a disease develops immunity, the condition is known as **acquired immunity**; this may be further subdivided into active and passive immunity.

Active immunity may be brought about in a number of ways. An individual having suffered from an attack of one of the infectious diseases, such as smallpox, becomes immune to subsequent attacks; the intensity and duration of this immunity will vary with different diseases and different individuals. Thus, in smallpox immunity is almost absolute; on the other hand, with cholera, and particularly with erysipelas, the duration of the period is short and the degree of immunity never very great. In erysipelas some practitioners believe that one attack predisposes to a second, thus indicating that instead of immunity there may be increased susceptibility.

Acquired immunity may also be brought about by inoculation. The inoculation may be made with attenuated microorganisms, or with such small doses of virulent bacteria that the disease is not induced; by gradually increasing the dose the animal becomes resistant to a quantity of the infectious agent that at first would have proved rapidly fatal. As examples of immunity induced by inoculation with attenuated organisms, the protection afforded to sheep by inoculation with anthrax bacilli, made less virulent by cultivation at high temperatures, may be cited. Although at present we are not certain what organisms—vegetable or animal—are active in cowpox, vaccinia, or smallpox, we are probably justified in believing that vaccination induces a form of immunity properly classified here.

It appears to have been demonstrated that the tubercle bacillus normally producing tuberculosis in cattle is most virulent for those animals, the bacillus producing tuberculosis in chickens most virulent for chickens, and the same rule applies to the bacilli causing tuberculosis in cold-blooded animals. Recent experiments seem to indicate that it

[1] "Jour. of Med. Research," vol. xiii, p. 305.

may be possible to immunize one species by the use of tubercle bacilli highly virulent for another but less so for the zoologic group experimented upon; working along this line, Pearson and Gilliland have succeeded in producing a certain degree of immunity in bovines by the use of tubercle bacilli of human origin.

Again, immunity may be secured by the use of bacterial products without using the living organisms themselves. The substances utilized for this purpose may be filtered toxins, derived from actively growing virulent organisms, or the cultures may be sterilized at temperatures (55° to 65° C.) so low that the toxins and proteid constituents of the bacterial cell are not destroyed and the sterile fluid may be injected subcutaneously or intraperitoneally. Haffkine's method of immunizing against plague consists in the subcutaneous injection of 1 to 3 c.c. of a bouillon culture of the bacillus killed by exposure to 70° C. for one hour. Wright's antityphoid inoculations consist of 1 c.c. of a heat-killed bouillon culture of the bacilli. Immunization against and treatment of, tuberculosis by chemical products of tubercle bacilli (tuberculosis), while not fulfilling expectations, has yielded in some instances promising results.[1] The use of a sterile filtrate for inducing immunity is the method at present in vogue for immunizing animals in the preparation of diphtheria antitoxin.[2] A certain degree of immunity may be induced by feeding animals on bacterial products, or even the bacteria themselves. Löffler[3] has recently shown that desiccated bacteria subjected to dry heat at 150° C. are eminently adapted to immunization; he has also used similarly prepared serum. The fact that dry enzymes withstand relatively high temperatures suggested to Löffler the plan which he has followed with success.

It has been proposed to utilize the terms induced, artificial, or experimental immunity to cover immunity brought about by experiment or inoculation, and to limit the term acquired immunity to the immunity that follows an attack of disease.

Passive Immunity.—If an animal that has been rendered immune by some of the methods previously given be bled, and the blood, or the serum separated from the blood, injected into another animal not previously immunized, the second animal acquires a more or less temporary immunity, which has been designated—by reason of its temporary character—passive immunity.

The immunity of this animal is dependent upon the presence of antisubstances taken from an actively immune animal. These substances disappear with a rapidity that varies in different animals, and with immunity against different infections. The induction of this form of immunity becomes important because of our ability to utilize it in the prevention and treatment of disease. Thus, if a number of children be exposed to diphtheria, a temporary immunity in their bodies may be brought about by injecting into their tissues a sufficient quantity of immunizing serum. This renders them immune for the

[1] The literature of this subject can be traced from references given by Trudeau and Baldwin, "Amer. Jour. of the Med. Sci.," December, 1898, and January, 1899; see also "Report of the Henry Phipps Institute for the Study, Prevention and Treatment of Tuberculosis," vol. i, 1904.

[2] See chapter on Bacteriologic Technic.

[3] "Deutsche med. Woch.," Dec. 22, 1904.

time being, and they escape infection from a single exposure. Again, this kind of immunity forms a basis for the treatment of the disease already developed. As it is well known that tissues are damaged by toxins of bacteria, any agent having a tendency to prevent this action becomes efficacious in the treatment of the disease: hence, knowing that a child is already infected by the diphtheria bacillus, the toxins being produced may be neutralized by introducing into the circulation of the patient a sufficient quantity of the antitoxin removed from an animal that has been actively immunized. Upon this basis rests the present serum therapy of diphtheria and related infections.

Local Immunity.—It has been shown that if the ear of a rabbit has been inoculated with the streptococcus of erysipelas and the animal has recovered, a subsequent inoculation, made simultaneously upon both ears, will be followed by a more active inflammation in the ear that has not been previously inoculated. It is also known that granulation tissue is more resistant to the inroads of infection than the normal tissue of the part involved. Both these facts indicate the presence of a resistance more or less restricted to limited areas. Whether this resistance is due to the presence of inflammatory products or to some peculiar anti-body not diffused by the circulating fluids has not been determined.

A careful study of the problems in immunity shows that for the successful prevention or cure of bacterial diseases it is necessary to recognize two distinct groups, which, however, undoubtedly overlap each other. In one of these the dominant symptoms and lesions are due to the toxic action of extracellular poisons; this is especially true of diphtheria and tetanus. In diseases belonging to this class the immunity depends upon neutralizing the extracellular toxins and need not be specifically directed toward destruction of the organism. In this class protection depends upon what has been called **antitoxic immunity.** In a second group of diseases the extracellular toxins are of far less importance than those poisons which develop and are retained, during the life of a germ, within the protoplasm of the bacterial cell. In diseases due to bacteria belonging to this class (typhoid, cholera, etc.) destruction of the germ or at least neutralization of the endotoxin is necessary to accomplish the desired result. The antagonism is directed toward the bacterial cell; the germ must be prevented from multiplying, and in order to accomplish this a **bacteriolytic immunity** is necessary.

Theories of Immunity.—As far back as the early years of the eighteenth century it was known in Europe that the Turks inoculated their children with smallpox matter, in the hope of bringing on a mild attack of the disease and thereby inducing an immunity. To Lady Mary Wortley Montague belongs the honor of first calling serious attention to this practice, in a letter addressed to her friends in England, and dated March 23, 1718. In this letter is described the inoculation of her young son with smallpox matter. Jenner's remarkable discovery of the immunity conferred by the cow-pox virus shortly followed. The more definite knowledge of the causes of disease afforded by the demonstration of bacteria as essential agents in the production of many affections promised a new field of research, which, during the last decade, has yielded so abundantly that it now becomes possible more fully to interpret many facts previously unappreciated or totally obscure

The exhaustion, accumulation, and related theories. Klebs and, at one time, Pasteur believed that, in the first attack, something in the system essential to the life of the organism became exhausted, and the germ died. A recurrence of the disease wholly depended upon a renewal of this substance, and in the interim the person possessed an immunity to the disease. Chauveau, supported by many eminent bacteriologists, believed that the immunity depended upon the accumulation in the system of bacterial products that, having arrived at a certain degree of concentration, are incompatible with germ life.

Grawitz explained the induction of immunity by assuming that in infectious diseases a conflict between the cells of the body and the germs of disease ensues immediately upon the introduction of the latter into the tissues. If the cells are victorious in the combat, they ever after should possess increased power of resistance to this particular germ, and, in fact, be able to destroy it immediately upon its entrance into the tissues.

Fig. 55.—Cells from Exudate, Case of Empyema. The large hyaline cells (macrophagocytes) contain many pneumococci.

Büchner promulgated an explanation that was a slight modification of Grawitz's hypothesis. He assumed that in every infection there is an inflammatory reaction at the point where the germs localize, and that an alteration in the cells is thereby induced that subsequently enables the cells of the economy to resist and destroy that particular germ.

Metchnikoff next advanced the theory of **phagocytosis,** which he has enthusiastically defended through all the controversy that has arisen since its introduction, and, by adapting it to newly acquired facts, has succeeded in maintaining for it a position in the first rank among the various explanations that have been offered for the phenomena of immunity.[1] He believes that the ameboid cells of the body take into their substance the bacteria, just as they would a particle of foreign matter or an article of food, and, appropriating a portion to their own use, throw off the remainder into the blood, to be carried to and excreted by the emunctories. Although many cells of the body are competent to perform the function of phagocytosis, the typical phagocytes are: (1) The microphagocyte of Metchnikoff, identical with the neutrophile and amphophile cells of Ehrlich, or the finely granular oxyphile cell of Kanthack and Hardy; (2) the macrophago-

[1] A full presentation of Metchnikoff's views will be found in his work entitled "Immunity in Infectious Disease," 1904, English translation.

cyte of Metchnikoff, or large lymphocyte of Ehrlich, or hyaline cell of Kanthack and Hardy;[1] (3) endothelium, particularly the endothelial cells of the blood capillaries, and partly, although to a somewhat unknown extent, the endothelium of the lymphatics, and even large lymph-spaces, such as the serous membranes; (4) other mesoblastic cells, particularly during active proliferation or when subjected to irritation. In this last group belong the polyblasts and fibroblasts of embryonic and granulation tissues, and possibly similar cells produced under other circumstances.[2] Leishmann[3] has devised a method of measuring the phagocytic power of leukocytes. Wright and Douglas[4] have shown that in the blood-plasma and serum there are certain substances which in some way not yet accurately determined so act upon and alter the bacteria that phagocytosis more readily can take place. The bodies possessing this quality are called **opsonins**; they are rendered inert by temperatures of 60° C. to 65° C.

Nuttall,[5] Büchner,[6] and others having demonstrated the bacterial powers of the blood, Fodor was led to believe that immunity depended upon the presence in the body-fluids of materials destructive to the bacteria. Büchner and Hankin showed the presence in the blood of certain bodies they called *alexins*, and upon the activity of which immunity was believed to depend. It was shown, however, that the bactericidal properties of the various sera did not prevent the cultivation of bacteria upon them, nor, when such sera were taken from animals naturally immune and injected into susceptible animals, did they produce immunity. Metchnikoff held that the protective agencies in the sera arose from *phagolysis* (dissolution of the leukocytes) and the retention in the blood of the anti-infectious agent normally produced and found within the phagocytic cells. As a result of these observations there has gradually been evolved the **cellulohumoral theory** of immunity, which best accords with the facts established by experience or elucidated by research. This theory presumes that there are certain "*anti-bodies*" present in the cells and body-juices of an animal, no matter what form of immunity it may possess. As the name indicates, the cellulohumoral theory is based upon the belief that these substances are present in the body-juices as well as in the cells, while at the same time the tendency of investigators is to believe that these protective agents are produced by the somatic cells.

In 1897 Ehrlich announced his hypothesis, known as the **side-chain theory of immunity,** which has largely replaced the older views. While necessarily somewhat complex, it best explains many facts which other theories less clearly elucidated. Like Metchnikoff's theory of phagocytosis, Ehrlich's explanation is based upon normal nutritional processes in the body-cells. The former observer held that the leukocyte obtained its nutrition, at least in part, by englobulating food particles coming

[1] For classification and description of these leukocytes see table in chapter on Pathology of the Blood, Part III, Chapter I.

[2] For further consideration of phagocytosis the reader is referred to the article on Inflammation.

[3] "Brit. Med. Jour.," Jan. 11, 1902, p. 73.

[4] "Proceedings of the Royal Society," vol. 72, p. 357, also vol. 73, 1904, p. 378, and "Lancet," 1904, vol. ii, p. 1138.

[5] "Zeit. f. Hyg.," Bd. iv, p. 353.

[6] "Centralbl. f. Bakt.," Bd. v, p. 821.

within its reach, and this physiologic attribute of the cell became a protective mechanism in the destruction of bacteria. Ehrlich assumes that each cell possesses special chemic affinities which enable it to attract and attach to itself substances necessary for its nutrition; he compares these hypothetic bodies to the side-chains of certain chemicals having highly complex molecules. Diagrams illustrating the theory necessarily convey the impression that these side-chains are morphologic entities; such, however, is not the case. The structure of cells gives no hint of the presence of such bodies; they are chemic and not morphologic parts of the cells. It is supposed that in the normal nutrition of the cell, each food molecule that it assimilates enters by a different chemic combination with the cell protoplasm. This path by which the cell takes food constitutes what Ehrlich originally termed a side-chain, but which later he designated a **receptor**; necessarily the multitudinous receptors by which each cell obtains its nutrition must differ chemically, and the receptors of different cells must also be dissimilar. Toxins circulating in the blood are attached to the cell by the same mechanism as the nutritional elements; in other words, by the receptors. If the quantity of the poison be sufficient, the cell is destroyed. If, on the other hand, the poison be in small amounts, the particular receptors only are affected. Weigert called attention to the fact that in the process of repair the tissues always manifest a tendency to exceed the absolute requirements for the restitution of structure, and Ehrlich applied this observation to explain the formation of antitoxin. If a given receptor or set of receptors is constantly attacked, the tendency of the cell will be to reproduce these structures in increasing quantities. Eventually the surplus receptors are thrown off into the body-fluids with which they circulate. If the poison enter the circulation, the fluids of which are already surcharged with suitable combining elements (receptors), it becomes at once attached to these substances, is neutralized, and the cells escape. The free receptors circulating in the blood and possessing the power to neutralize toxins are the **antitoxins.**

It will be observed that the theory just outlined offers an explanation for (1) natural immunity in which it is possible to conceive that (*a*) the cells of the immune animal possess no receptors suitable for the particular poison, or, (*b*) the body-fluids of the animal may be surcharged with receptors which anchor the incoming poison and prevent it from attacking the cell. (2) It gives a satisfactory reason for the occurrence of acquired immunity, whether produced by an attack of the disease, the administration of bacterial products, dead or living bacteria, or by other methods of vaccination. (3) It elucidates the occurrence of passive immunity produced by injecting the blood or serum of an immune into a non-immune animal. (4) It explains the presence of antitoxin in the blood and gives an adequate reason for its continued manufacture by the cells. (5) The receptors attacked are those having special affinities for the poisons influencing them, and as these only are regenerated, it becomes evident why antitoxic substances possess such striking specificity—the antitoxin of diphtheria neutralizing the poison of that organism, the antitoxin of tetanus neutralizing the poison of the tetanus bacillus, but neither antitoxin exerting any specific influence upon the poison produced by the other organism. (6) Aside from its application to the problem of immunity, this theory also offers

an explanation for the well-known fact that infectious diseases are characterized by the occurrence of a more or less definite time between exposure to infection and the development of symptoms; this is ordinarily called the period of incubation, and corresponds to the time necessary for the specific organism to grow and produce its poison and permit this toxin to attack the cells with sufficient intensity to disturb their function and give rise to symptoms.

Ehrlich found that he could immunize animals to such poisons as abrin and ricin, and that the process of tissue immunization is not restricted to antagonism against bacterial poisons alone. It has been shown by a number of observers that it is possible for the toxin molecule to manifest a great reduction, amounting in some instances almost to an entire loss of its toxic properties, although it still retains its power to combine with the antitoxin. Such toxins are called **toxoids.** The demonstration of this fact led Ehrlich to the conception that the toxin molecule possessed two groups; one by which union with the cell occurred, **haptophore group,** and the other by which the destructive action of the toxin is manifested—the **toxophore group.** The combination between toxin and antitoxin resembles chemic union in that it is more rapid at high temperatures than low, and less intimate in weak than in concentrated solutions; further, it follows the law of multiples, as shown by the fact that if the quantity of antitoxin necessary to neutralize the minimum lethal dose of the toxin is increased ten times and mixed with ten minimum lethal doses, neutralization will be complete.[1]

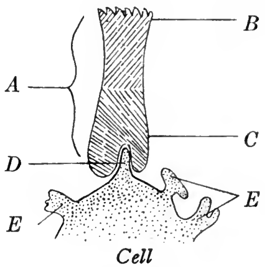


FIG. 56.—DIAGRAM ILLUSTRATING EHRLICH'S VIEWS CONCERNING THE UNION BETWEEN TOXIN AND CELL.

A *Toxin molecule*, of which B is the *toxophore group* and C the *haptophore group*. D, Cell *receptor*. E, E, *Receptors* not adapted to combination with the particular toxin A, but might combine with other toxins possessing appropriate haptophore groups.

It will be seen that the foregoing summary of Ehrlich's views explains the phenomena of antitoxic immunity, but for reasons given below must be modified in order to elucidate bacteriolytic immunity. Recent studies in cytolysis, especially hemolysis, have shown that the process by which the protective forces of the body antagonize foreign blood-cells operates in a manner essentially identical with the methods by which bacteria are destroyed. It is evident that entirely different agents accomplish the destruction, but their methods of operation appear to be identical. In consideration of this type of immunity it is to be borne in mind that the statements which follow apply to bacteriolysis and cytolysis, bacteriolytic and cytolytic immunities. As already stated, Fodor, Nuttall, Büchner, and others, have shown that blood-serum possesses the power of destroying bacteria. Büchner attributed this quality to substances he called alexins. It was first demonstrated by Bordet that if bacteriolytic blood or serum be subjected to a temperature of 56° C. for half an hour, the cytolytic or bacteriolytic property was lost and the serum rendered inactive. If to this inactivated serum there was added a small quantity of blood or serum from an animal of the same species not immunized to the par-

[1] For standardizing antitoxin see chapter on Bacteriologic Technic.

ticular germ or cell upon which the experiment was being conducted, the inactivated fluid reacquired its property of destroying the germ or other cell; in fact, became reactivated. This experiment clearly demonstrated that cytolytic and bacteriolytic activities depend, in each instance, upon the presence of two substances, one of which is destroyed at 56° C. (thermolabile body), the other resisting higher temperatures (thermostable). The substance present in normal blood and easily rendered inert by heat is called the complement, alexin, cytase or addiment. In the following description the term **complement** will be used. The heat-resisting substance is known as the intermediary or intermediate body, immune body, substance sensibilisatrice, amboceptor, fixator, sensitizer, philocytase, copula, desmon, preparator, and immunisin; of these, **amboceptor** and **immune body** are commonly employed. For the production of cytolysis or bacteriolysis it is necessary for the cell to possess a receptor the molecular constitution of which is adapted to combination with the cytophile haptophoric group of the immune body, the latter in turn combining by its complementophile group with the haptophoric group of the complement; the zymotic group of the complement acts through the chain formed by the foregoing combination. The absence of any one of these conditions prevents the occurrence of cytolysis. A solution containing both immune body and complement may be deprived of either, leaving the other, which, if injected into an animal, gives rise to an antibody possessing the power of antagonizing or neutralizing the substance used in the injection. As already stated, serum heated to 55° or 56° C. is inactivated as a result of destruction of the complement; it still contains, however, the immune body. The removal of the latter substance from the mixture containing both is somewhat more complex, but may be accomplished in the following manner: If the serum of a rabbit immunized to bovine red blood-cells be mixed with the bovine erythrocytes at ordinary temperatures, hemolysis occurs; if, however, the mixture is kept at or about 0° C., the immune body combines with the cells, hemolysis being prevented by the fact that, at this temperature, the complement is inactive. The red cells may be removed by sedimentation, and if redistributed in a solution containing complement, at the proper temperature, promptly undergo hemolysis. It can be shown that the fluid from which the red cells were removed still retains the complement. The method by which anticomplement and anti-immune body intervene in the prevention of hemolysis is indicated by the accompanying diagram (see Figs. 58 and 59).

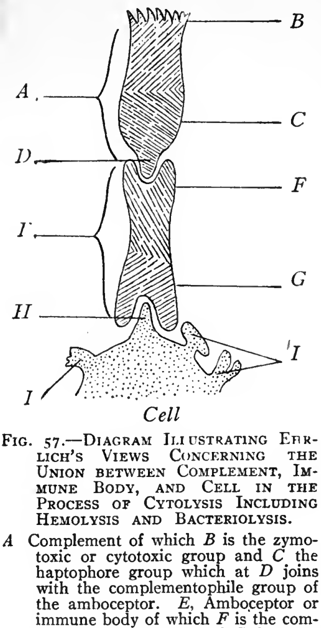


FIG. 57.—DIAGRAM ILLUSTRATING EHRLICH'S VIEWS CONCERNING THE UNION BETWEEN COMPLEMENT, IMMUNE BODY, AND CELL IN THE PROCESS OF CYTOLYSIS INCLUDING HEMOLYSIS AND BACTERIOLYSIS.

A Complement of which *B* is the zymotoxic or cytotoxic group and *C* the haptophore group which at *D* joins with the complementophile group of the amboceptor. *E*, Amboceptor or immune body of which *F* is the complementophile group and *G* the cytophile haptophoric group. *H*, Cell receptor. *I*, *I*, Receptors not adapted to combination with the particular immune body *E*, but might combine with other amboceptors possessing appropriate cytophile haptophoric groups.

The scope of this work does not permit a discussion of the multiplicity of complement or the limitations within which the immune body is specific. Experiments seem to indicate that there is more than one complement and that the immune body within certain limits is specific.[1] With regard to the source of the complement, Metchnikoff and his students strongly maintain that it is derived from the leukocytes; assuming its production by the microphagocyte or the macrophagocyte, he recognizes two types, the microcytase and the macrocytase. Abbott and Bergey have shown that alcohol may decrease or attenuate the

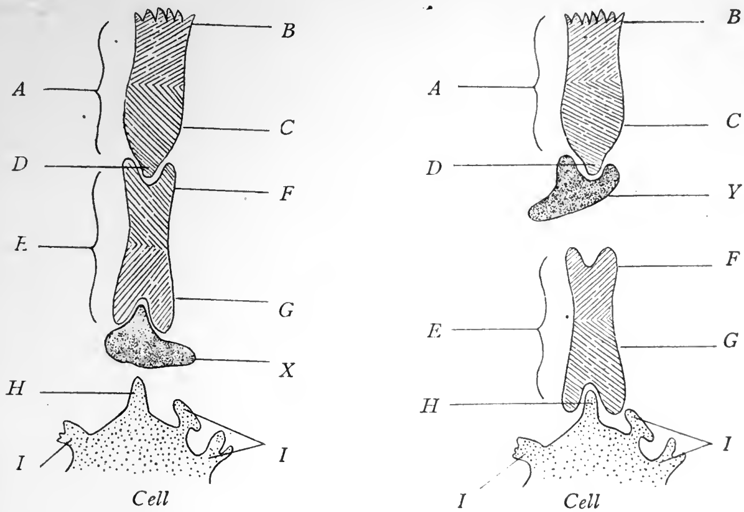


FIG. 58. FIG. 59.

Diagram illustrating Ehrlich's views concerning the action of (Fig. 58) anti-immune body, and (Fig. 59) anti-complement in preventing cytolysis, including hemolysis and bacteriolysis. *X* (Fig. 58), Anti-immune body or anti-amboceptor. *Y* (Fig. 59), Anti-complement. The other letters have the same significance in both figures.

Complement of which *B* is the zymotoxic or cytotoxic group and *C* the haptophore group, which in the first figure combines at *D* with the complementophile group of the amboceptor or immune body; in the second figure this combination is prevented by the intervention of the anticomplement *Y*. *E*, Immune body or amboceptor, of which *F* is the complementophile group and *G* the cytophile haptophoric group which in the second figure combines with the cell receptor *H*; in the first figure this combination is prevented by the intervention of the anti-immune body or anti-amboceptor *X*. *I*, *I*, Receptors not adapted to combination with the particular immune body *E*, but might join other amboceptors having appropriate cytophile haptophoric groups.

It will be seen that either anti-amboceptor or anti-complement prevents cytolysis, including hemolysis and bacteriolysis, by interfering with the combination of complement, immune body, and cell receptor, all three of which must unite in order to act on the body cell or germ.

complement. Ehrlich and Morgenroth found that phosphorus produced a similar action. Nolf, Müller, and others have shown that it is possible to increase the complement.[2] Longcope[3] has demonstrated that in normal individuals fluctuations in the bacteriolytic complement of the

[1] Literature bearing on multiplicity of complements and specificity of immune bodies is widely distributed. In addition to the references given on preceding pages see Pearce, "Albany Med. Annals," Aug., 1904; also Longcope's article cited below, and Woltmann, "Jour. of Exp. Med.," vol. vii, No. 2.

[2] For interesting experiments on this subject and citations from literature, see Sweet, "Univ. of Penna. Med. Bull.," December, 1902.

[3] "University of Penna. Med. Bull.," November, 1902.

blood occurs, and that in many chronic affections, such as nephritis, cirrhosis of the liver, and diabetes, there is a marked decrease in the complement, and that terminal and agonal infections are probably due to this fact.

Welch[1] has made a most suggestive extension of Ehrlich's receptor theory; he inquires whether it would not be possible for the living germ to react to the body-cells and juices, just as Ehrlich's views indicate that the body-cells are led to produce antisubstances by stimuli coming from the bacterial poisons. This implies that the bacterial cells are possessed of receptors which, when damaged by combination with haptophore groups produced in the tissues of the host, would lead to reaction on the part of the germ which in turn might produce and liberate receptors in excess, just as the animal cells are supposed to do. This suggestive hypothesis explains how it is possible to augment the virulence of a given germ by successive inoculation into animals. Walker[2] has shown that bacteria cultivated on immune sera become more virulent, thus indicating that something in the culture medium stimulates the germ, giving rise to increased toxin production or the elaboration of poison possessing heightened toxicity.

Pfeiffer found that if cholera spirilla were introduced into the peritoneal cavity of rabbits immunized to that organism the bacteria became motionless, collected in groups (agglutination), and finally dissolved (bacteriolysis). This observation (Pfeiffer's phenomenon) was the starting-point of many experimental studies, and it was thought for a time that **agglutination** was a necessary part of bacteriolysis; this is now known not to be the case. Although agglutination occurs in various forms of cytolysis, the **agglutinins** resist temperatures (60° C.) destructive to the complements active in bacteriolysis. A serum that is both agglutinative and bacteriolytic may be deprived of the latter property without loss of the former. It has been shown that agglutinins possess a *haptophore* and an *agglutinophore group*, and that the cells (bacterial or somatic) influenced by these agents contain an *agglutinable substance* which in turn possesses two haptophore groups. Development of agglutinins in the blood of patients suffering from certain diseases has been shown to possess high diagnostic value, particularly in typhoid,[3] paratyphoid, and Malta fevers. It has been found that the blood-serum in malaria contains agglutinins for the erythrocytes of the noninfected, and that under certain conditions agglutinins for animal parasites (trypanosomes) may develop.

Precipitins.—If an animal receives subcutaneous or intra-abdominal injections of the cell-free serum of an animal of a different species, or the expressed juices of the tissues of the second animal, or egg-albumen, peptone, milk or whey, or even urine, there develop in the animal experimented upon substances which, when added to clear fluids containing minute quantities of the substance with which the animal was injected, give rise to a precipitate. The delicacy and extreme sensitiveness of

[1] Huxley Lecture on Recent Studies on Immunity, reference in foot-note on page 94.

[2] "Jour. of Pathology," March, 1902.

[3] For method of Widal's test in the diagnosis of typhoid fever see chapter on Bacteriologic Technic. Review of literature on the subject by Rosenberger, Publications from the Laboratories of the Jefferson Medical College Hospital, vol. i, 1904.

this reaction are among the striking additions to organic chemistry. These agents resist 60° C., but are rendered inactive by temperatures near 70° C. Within certain limits the action of precipitins approaches specificity. The serum of an animal immunized to human albumens reacts, although with less intensity, to the serum of the higher ape; rabbits immunized to chicken serum yield a precipitin that also reacts with pigeons, and animals immunized with albumen derived from the egg of the chick produce sera containing precipitins for the egg-albumen of closely related birds. Precipitins are useful for the identification of blood in medicolegal cases and may be used for the recognition of horse-meat and dog-meat in sausages, and are also of value in showing the relation existing between closely allied animal species.[1]

[1] For literature of precipitins see Nuttall, "Blood Immunity and Blood Relationship," 1904. The medicolegal value of the test is discussed by Nuttall, also Ewing and Strauss, "Medical News," Nov. 7 and 14, 1903.

CHAPTER V.

BACTERIA AS CAUSES OF DISEASE.—(Continued.)

THE INFECTIONS.

PATHOGENIC SCHIZOMYCETES

Morbid Processes Due to Disease-producing Bacteria.

The **schizomycetes** or **bacteria** include the largest number of vegetable organisms producing disease. Of the many classifications dividing the larger group into smaller subclasses, none has been fully satisfactory; the most convenient division is based upon morphologic peculiarities, which, by taking some liberties, permits, the recognition of three more or less distinct groups: (I) Cocci; (II) bacilli; (III) spirilla.

I. *Cocci.*—Spheric, slightly ovoid, or lancet-shaped bacteria, which reproduce by binary division, and occasionally by the formation of arthrospores.

The cocci form such complex varieties that a further subdivision will be necessary to facilitate our study of them:

By number	Monococci. Diplococci. Tetracocci.	By arrangement	Streptococci. Micrococci (staphylococci). Ascococci. Sarcinæ.

Varieties.—Monococci: cocci not definitely associated in any manner with one another. Diplococci: cocci associated in pairs. Tetracocci: cocci associated in fours. Streptococci: cocci arranged in chains, which may contain thirty or more elements. Micrococci (staphylococci): cocci growing in irregular masses; the individual elements are embedded in a gelatin-like substance elaborated by the organisms. Ascococci: cocci associated in circular or globular masses (zooglea) held together by a gelatinous substance. Sarcinæ: cocci arranged in packets or cubes of eight or more elements.

II. *Bacilli.*—Rod-shaped organisms, motile or nonmotile, rigid or flexible. The organism formerly described as a bacterium is included in this class.

III. *Spirilla.*—It is necessary to divide the spirilla into two groups. In one of these the spirals are rigid and relatively short; the spirillum of Asiatic cholera possesses these characters. In the second type the organisms are longer, more flexible, and the disparity between length and thickness much greater than in the first type; organisms possessing these characters have been found in relapsing fever, and more recently in syphilis. There are reasons for believing that the long, undulating, actively flexible spirils are not bacteria but properly belong with the unicellular animal parasites. This view is further supported by the fact that in neither relapsing fever nor syphilis has the parasite been cultivated.

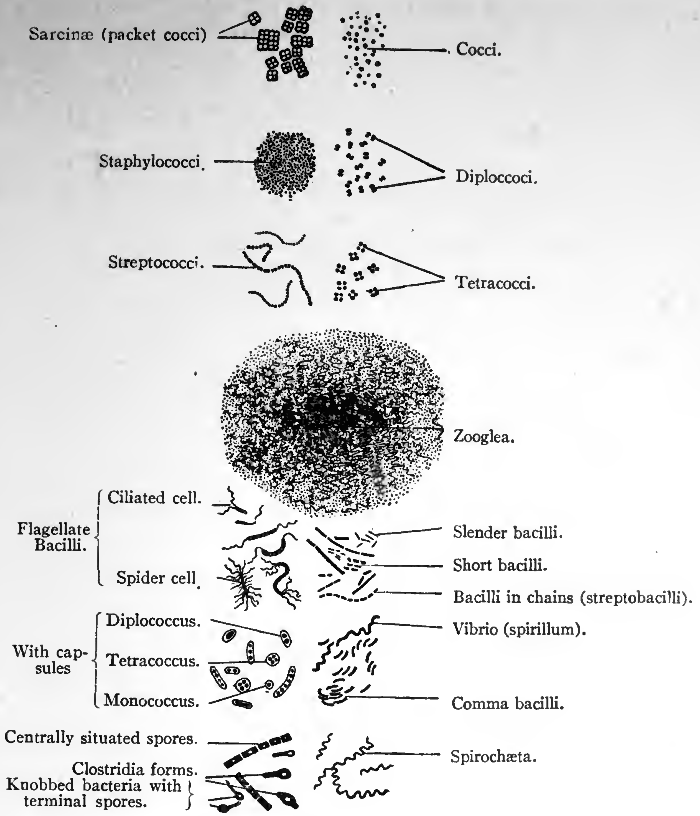


FIG. 60.—DIAGRAM ILLUSTRATING THE NOMENCLATURE OF SCHIZOMYCETES BASED UPON THEIR MORPHOLOGY.—(*After Schenk.*) × about 700 diameters.

Sarcinæ include the packet cocci; cocci arranged, in more or less cuboid shapes, as multiples of four. Each packet contains 8, 16, 32, or more units. The cocci proper, include those named by the number commonly in the group, as: (*a*) Monococci, or cocci with no special arrangement or grouping; with these we include the staphylococci. (*b*) Diplococci, or cocci grouped in pairs. (*c*) Tetracocci cocci grouped in fours. The second method of naming is by arrangement, as: (*A*) Streptococci, cocci arranged in chains; (*B*) ascococci, or encapsulated grouped cocci; (*C*) staphylococci, or cocci presumed to be arranged as grapes in a cluster. The student will fail to detect, under the microscope, the difference between the micrococci and the staphylococci. The term "zooglea" is applied to agminated masses of microbes, usually cocci, embedded in a gluelike mass of gelatinous material elaborated by the microbe. The ciliated and spider cells are flagellate bacteria. The spirochæta are flexible spirals, such as the organism of relapsing fever.

PATHOGENIC COCCI.

The **gonococcus**[1] (Neisser, 1879) is a roll or biscuit-shaped, non-motile, aerobic diplococcus, 0.8 μ to 1.6 μ in diameter. Cultures may be obtained on human blood-serum, or on media containing that substance

[1] Muir and Ritchie, American edition, edited by Harris, give references to important articles up to 1902. Pinto, "Jour. de Phys. et de Path. Gen.," Nov. 15, 1904, p. 1058, "Cultivation, Toxins, etc." Elting, "Albany Med. Annals," March, 1900. Wynn, "Lancet," Feb. 11, 1905, "General Gonococcus Infection." Kimball, "Med. Record," Nov. 14, 1903, "Gonococcus Infections in Infants." Krause, "Berl. klin. Woch.," May 9, 1904, "Gonorrheal Sepsis." Holt, "N. Y. Med. Jour.," March 18, 1905, "Gonococcus Infection in Children." Jeckstadt, Med. Diss. Königsberg, 1904, "Cultural Characters and Diagnosis." McColgan

also on acid urine agar and blood-smeared agar; Wertheim's medium[1] may be used. The organism develops slowly, appearing twenty-four to thirty-six hours after inoculation as a smooth, thin, grayish-yellow, moist film with ill-defined margins; later the margins become jagged with sharper definition. The optimum temperature is 33° C. to 37° C., the maximum 38° C., and the minimum 25° C.

Demonstration.—Make spreads and fix in the usual manner; stain in alcoholic solution of methylene-blue five to fifteen minutes; wash with water and restain for the same length of time, using a saturated alcoholic solution of eosin. Wash in water, dry and mount. The nuclei of the pus corpuscles and the gonococci are blue, protoplasm of the pus cells pink. As the organism does not stain by Gram's method the following technic may be found useful: Stain by Gram's method followed by dilute carbol-fuchsin (1 to 10). Wash in water, dry and mount; the organisms stained by Gram's method are not gonococci, those taking the fuchsin may be; positive identification is possible by cultivation methods only. It also may be stained by any of the basic anilin dyes, especially Löffler's methylene-blue.

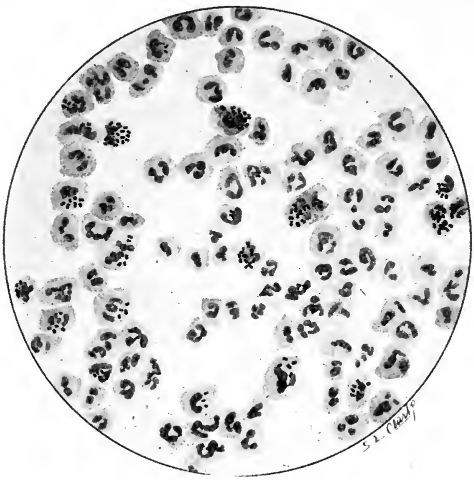


FIG. 61.—GONOCOCCUS.
Film from urethral pus. In this specimen practically all the organisms are intracellular; frequently extracellular gonococci are present.

Pathogenesis.—Under ordinary conditions the gonococcus is pathogenic for the human species only; it produces **local infections** on mucous membranes, particularly the urethra, from which it may extend to the bladder, ureters and renal pelves, seminal vesicles, vas, and epididymis; it also causes prostatitis. In the female, vaginitis and vulvovaginitis, endocervicitis, endometritis, salpingitis, and peritonitis may be due to this organism. Gonorrheal peritonitis is particularly prone to occur in the vulvovaginal lesions due to gonococcus infections in children. Gonorrhea of the rectum is rare. Gonorrheal conjunctivitis, also called gonorrheal ophthalmia, is a particularly destructive process most common in the new-born, due to infection from the birth canal, but also resulting from accidental conveyance of gonococci to the conjunctiva. Nasal, oral, and pharyngeal gonorrhea are rare. The lesion on the mucous membrane may be acute, subacute, or chronic; in the acute

and Cooper, "Jour. Amer. Med. Assoc.," April 2, 1904, p. 877, "Gonococcemia, Arthritis, Inflammation of the Tendon Sheaths." Harris and Haskell, "Johns Hopkins Hospital Bulletin," December, 1904, and Busquet and Bichelonne, "Gonococcus Infection of Muscles." Heller. "Berl. klin. Woch.," June 9, 1904, "Gonorrheal Phlebitis." Nenéprier, "Soc. Méd. des Hôp. Paris," June 23, 1904, "Multiple Neuritis in Gonorrhea."

[1] See chapter on Bacteriologic Technic.

form the gonococci are particularly abundant in the epithelial cells and migrating leukocytes, particularly the polymorphonuclears, but are also found extracellular; in the chronic lesions the organism is less abundant. The gonococcus has been definitely accepted as a pus-producing organism, and in connective tissues may give rise to distinct abscesses, among which should be mentioned peri-urethral abscess and prostatic suppuration.

Systemic infection by the gonococcus. The organism in pure culture has been obtained from the blood during life; usually it enters from infections of the genital organs, although **gonococcemia** secondary to conjunctival gonorrhea has been reported. Pinto and also Christmas have shown that the organism produces a toxin to which some of the systemic phenomena may be due. Entering the circulation the gonococcus may give rise to endocarditis, endarteritis or endophlebitis, inflammations of the joints, pericardium, or pleura. Cases of gonococcal pyemia have been reported. According to Heller, there are 26 cases of gonorrheal phlebitis on record. Joint affections are usually monarticular, but may be polyarticular. The joints most frequently affected are the knee, elbow, and wrist, in the order named; involvement of the smaller joints is not common. Usually the lesion stops short of suppuration; a tendency to fibrous ankylosis is not infrequently present.[1]

The **Diplococcus pneumoniæ**[2] (Fränkel, 1884) is a lancet-shaped, non-motile, aerobic coccus, usually associated in pairs, end to end, and possessing a capsule which is lost during cultivation. In size the organism varies; its usual maximum diameter is about 1 μ; chains containing four to eight cocci occur. It may be cultivated on the ordinary

[1] For pathology of inflammation of the mucous membranes see chapter on that subject; also article on Acute Malignant Endocarditis in chapter on Diseases of the Heart.

[2] See foot-note, p. 81. Rosenberger, "Amer. Jour. of the Med. Sci.," August, 1903, article on "Bacteriology of the Blood," with literature of Pneumococcemia. Rosenau, "Jour. Amer. Med. Assoc.," March 18, 1905, p. 871. Lesieur, "Jour. of Physiol.," Nov. 15, 1903. Steuertz, "Zeit. f. klin. Med.," 1904, Bd. 52, p. 422. Wolstein, "Jour. of Exper. Med.," vol. vi, p. 391, "Bacteriology of Broncho- and Lobar Pneumonia in Infancy." Hiss, Ibid., p. 317, "Differentiation of Pneumococcus and Streptococcus." Mathews, "Annals of Surgery," November, 1904, "Pneumococcus Peritonitis." Anders, "Amer. Med.," March 18, 1905, p. 431, "Cholecystitis Due to the Pneumococcus." Tizzoni and Panichi, "Centralbl. f. Bakt.," 1905 (ref.), Bd. xxxvi, p. 25, "Latency of Pneumococci in the Blood." Pätzold, "Beitr. z. klin. Chir.," 1904, xliii, "Necrosis of the Muscle in Pneumococcal Infection." Foulerton, "Trans. Path. Soc. of London," 1902, vol. 53, p. 286, "Pneumococci Gastritis." Rossi, "Gaz. degli Osped. e delle Clin.," Feb. 5, 1905, "Diplococcemia." Bullard and Sims, "Boston Med. and Surg. Jour.," Dec. 15, 1904, "Diffuse Encephalitis showing the Pneumococcus." Davies and Brown, "Lancet," Oct. 8, 1904, p. 1017, "Pneumococcic Pyemia," with full bibliography. Baduel, "La Rif. Med.," June 29, 1904, "Pneumococcal Polyarthritis." Bithell, "Jour. of Path. and Bact.," 1904, "Pneumococcus in Empyema." Tchistovitch, "Annales de l'Inst. Pasteur," May 25, 1904, "Pathogenesis of the Pneumococcus." Ghön, "Wien. klin. Woch.," March 10, 1904, p. 267, "Pneumococcal Peritonitis, Historical, Chemical, and Pathological Report," with bibliography. Duckworth and Marsh, "Clin. Soc. of London," Jan. 8, 1904, "Pneumococcal Peritonitis." Richardson, "Jour. of Boston Soc. of Med. Science," vol. v, p. 499, "Pseudo-pneumococci in Lobar Pneumonia." Spitta, "Brit. Med. Jour.," Nov. 15, 1902, p. 579, "Pneumococcic Infection." Slaughter, "Amer. Med.," April 18, 1903, p. 605, "Record of Forty Cases of Pneumococcic Arthritis."

media, but possesses a low vitality and grows best on media containing blood or blood-serum. The colonies are small, discrete, dew-like, with sharply defined edges not tending to coalesce but occasionally forming transparent moist films; does not liquefy gelatin. The optimum temperature is 37° C., maximum 42° C., minimum 20° C. to 22° C.

Demonstration.—The pneumococcus stains with the ordinary anilin dyes and by the usual methods; it is Gram-positive. Friedländer recommends staining the pneumococcus in tissues as follows: Make thin sections, remove the paraffin, and stain for twenty-four hours in an acid solution of gentian-violet, made by mixing 50 parts of a saturated alcoholic solution of gentian-violet, 100 parts of distilled water, and 10 parts of acetic acid. After staining, decolorize with a one per cent. solution of acetic acid in water for one or two minutes, dehydrate with alcohol, clear with oil of cloves, and mount.[1] The pneumococcus is often difficult to cultivate from body fluids or organs and is easiest obtained in pure culture by inoculating a rabbit or mouse, both of which animals are extremely susceptible. Media rich in sodium chlorid are ill adapted to its growth, and it has been suggested that sodium chlorid retention in croupous pneumonia is a part of nature's protective mechanism. In cultivation it rapidly loses virulence, requires frequent transplantation, and is best preserved in capillary tubes containing sterile rabbit's blood. The best medium for securing cultures is peptone bouillon containing eight per cent. glucose.

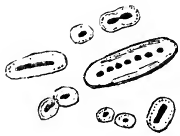


Fig. 62.—Diagram of the Diplococcus of Pneumonia Illustrating Relation of Capsule to the Contained Germ.—(*Coplin and Bevan.*)

Pathogenesis.—The pneumococcal infections in man may be local or general; locally it affects particularly the mucous and serous membranes and lungs.[2] It is a specific causative agent in many coryzas and may produce catarrhal or pseudo-membranous inflammations of the mucous membranes. It is a frequent cause of serous membrane inflammations, especially of the pleura; it also gives rise to peritonitis and sporadic meningitis. Instances of epidemic meningitis due to the pneumococcus are also on record. Otitis media and inflammation of the facial sinuses are not infrequently of pneumococcal origin. It occasionally infects wounds, and has been obtained by Boyd from abscesses in pure culture. In many individuals it is a constant inhabitant of the mouth and nose; from the latter cavity extension to the middle ear and meninges may occur. In a number of pneumococcal infections, especially croupous pneumonia, the organism enters the blood; in Rosenberger's collated cases of pneumonia, blood infection was present in fifty-three per cent.; once in the circulating blood the pneumococcus may give rise to arthritis, which is sometimes monarticular and sometimes polyarticular. Davies and Brown have tabulated 39 cases of pneumococcic pyemia. As a result of blood infection it may produce endocarditis, endarteritis, or thrombophlebitis. Ordinarily in pneumococcic infection a prompt leukocytosis occurs; in rapidly fatal

[1] For the demonstration of capsules, see Capsule Stains in chapter on Bacteriologic Technic.

[2] Its action on these structures is discussed in chapters on Diseases of the Mucous Membranes and Diseases of the Lungs.

cases there may be no leukocytic response, the number of leukocytes rapidly falling. With regard to the poisons produced by the pneumococcus much remains to be determined. Its short life on cultivation is not conducive to the production of toxins in sufficient quantity for experimental investigation. The Klemperers obtained a toxin (pneumotoxin), and the symptoms, lesions, and complications of pneumonia and other pneumococcic infections indicate that its action is exerted through the intervention of some poison which it produces. Animals can be immunized against the pneumococcus, but attempts to produce immunizing sera have been, on the whole, disappointing. Stuertz thought that in pneumococcic infections information as to prognosis might be obtained by inoculating animals. By using the sputum he found that in virulent cases of pneumonia mice succumbed in from six to eight hours; in the more chronic cases the animals survived two days.

The pneumococcus is also the cause of chronic inflammatory conditions, either catarrhal or pseudomembranous, affecting various mucosæ, but particularly the nose and bronchi. Tizzoni and Panichi have found that it may remain latent in the circulation for weeks or months.

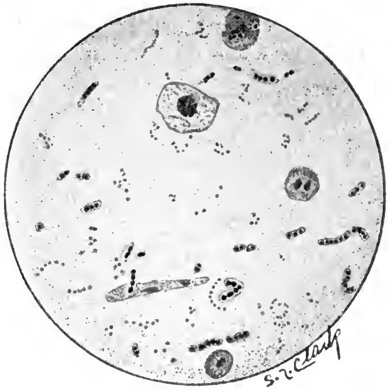


FIG. 63.—SPUTUM, CROUPOUS PNEUMONIA.
In the extreme upper part of field is a leukocyte showing chromatolysis but containing englobulated cocci. Below and slightly to the left of this cell is a squamous cell from the mouth. To the right of the latter and slightly below is a polymorphonuclear leukocyte, and in the extreme lower part of the field is a small hyaline cell. The field also contains numerous encapsulated pneumococci a few streptococci and unarranged cocci that can not be identified with accuracy.

The **Meningococcus or Diplococcus intracellularis meningitidis**[1] (Weichselbaum, 1887) possesses almost the exact morphology of the gonococcus and is also commonly found within the cells. It usually occurs in pairs or fours, and sometimes in short chains of four to six elements. It is non-motile, aerobic, cultivated with difficulty, and has a restricted temperature range at or near 37° C. It grows best on blood-

[1] See foot-note, p. 81. Councilman, Mallory, and Wright, "Epidemic Cerebrospinal Meningitis," Report of Board of Health of Massachusetts, 1898, full bibliography. Pinto, "Jour. de Phys. et Path. gén.," Nov. 15, 1904, p. 1058, "Its Relation to Other Diplococci." Warfield, "Univ. of Penna. Med. Bull.," July and Aug., 1903, "Endocarditis due to Meningococcus." Bettencourt and Franca, "Zeit. f. Hyg. u. Infekt.," 1904, Bd. 46, "Epidemic Meningitis." Schiff, "Centralbl. f. inn. Med.," June 4, 1898; also Mandoul, "Presse Med.," Feb. 11, 1905, p. 89, and Lord, "Centralbl. f. Bakt.," Oct. 9, 1903, p. 645, "Meningococcus in Nose in Health and Disease." Auché, "Revue Mens. des Mal. l'Enfance," Jan., 1904, "Diplococcus Meningitis in Children." Rist and Paris, "Arch. gen. de Med. Exp.," 1904, No. 8, p. 449, especially in chronic meningitis. Berg, "Med. Record," Sept. 10, 1904, "New York Epidemic," bibliography. Reuling, "Maryland Med. Jour.," June, 1904, careful study of case. Still, "Practitioner," Feb., 1905, p. 217, "Meningococcus in Infantile Paralysis," bibliography. Maragliano, "Gaz. Osped. et Clin.," 1905, No. 19, "Experimental Production of Meningitis from Nasal Infection." Nuttall and Hunter, "Brit. Med. Jour.," Sept. 21, 1901, on two types of the meningococcus. Fischer, "Pediatrics," Oct. 15, 1900.

serum or on Löffler's medium, on both of which it produces smooth, round, colorless, slightly lustrous colonies, the borders of which are usually sharply defined, although they may become confluent; maximum development occurs in six days and transplantation every two or three days is necessary. Growth on agar is scanty, in stroke cultures but two or three millimeters in width the surface moist and not granular. It clouds bouillon with the formation of a slightly viscid sediment. It grows feebly or not at all on gelatin and does not liquefy the medium.

Demonstration.—It stains with the usual anilin dyes, but its reaction to Gram is inconstant. For this and other reasons Nuttall and Hunter concluded there were two types, which they designated "A" and "B"; the latter is Gram-positive, grows luxuriantly on agar, producing viscid colonies; the growth on potato is also good. Type "A" is indefinite, usually negative to Gram, of feeble growth on agar and glycerin-agar; there is a slight invisible growth on potato. For staining sections Councilman, Mallory, and Wright recommend Unna's alkaline methylene-blue solutions (see p. 48) applied as follows: (1) Saturated aqueous solution of eosin, twenty minutes or longer; (2) wash in water; (3) alkaline methylene-blue (diluted), one or two hours; (4) wash in water; (5) differentiate in commercial alcohol followed by absolute alcohol; (6) clear in xylol; (7) mount in balsam. Spreads may be treated in the same way. Cultures are usually secured from fluid obtained by lumbar puncture, and while the fluid so obtained may appear, by staining methods, to contain a large number of organisms, culture experiments indicate that comparatively few of these are viable. For this reason a relatively large quantity of the fluid should be spread over the surface of the culture-medium.

Pathogenesis.—The meningococcus is generally admitted to be the cause of epidemic cerebrospinal fever.[1] Still has recently summarized the reported epidemics of infantile paralysis in which the meningococcus was found. It is sometimes present in sporadic cases of meningitis and infantile paralysis. It probably reaches the meninges from the nasal passages, in which it is occasionally found in health, but more frequently in meningitis; Maragliano has produced meningitis in rabbits by spraying cultures of the organism into the nasal cavity. The meningococcus is feebly pathogenic for mice, rabbits, guinea-pigs, and dogs.

Meningitis has been produced in the goat by intracranial inoculation. According to Lepierre, it produces a toxin (meningotoxin) which resembles the gonotoxin studied by Christmas. The meningococcus has been found in endocarditis.

The **Diplococcus rheumaticus**[2] (Poynton and Paine) occurs as paired cocci, 0.5 μ or slightly larger, and has been found in the joint fluids, synovial membrane, and endocardial lesions of acute articular rheumatism. It grows best in mixtures of bouillon and milk faintly acidified by lactic acid; it can also be cultivated on blood-smeared agar and blood-serum. On solid media the colonies are small, spherical, and granular. On milk it produces lactic and acetic acids, and on glucose and levulose media, acetic and valerianic acids. Walker and Ryffel

[1] See chapter on Diseases of the Nervous System.

[2] Practically all existing knowledge concerning this organism will be found in or may be traced from Poynton's article in "The Practitioner," July 1, 1904, p. 864. See also Triboulet and Coyon, "Rheumatisme Articulaire Aigue," 1901, and Beattie, "Jour. of Path. and Bact.," March, 1904, p. 272.

found that it produced formic acid and was strongly hemolytic. In liquid media it forms short chains, on blood and serum agar there is no irregularity in its arrangement. The organism stains, but not intensely, with the usual anilin dyes; it is Gram-negative.

Pathogenesis.—In rabbits the articular and cardiac lesions of acute rheumatism have been produced by intravenous injections of the organism; non-suppurative iritis occasionally occurs. Poynton has shown that monkeys are susceptible to the organism. It is identical with the Micrococcus rheumaticus, described by Walker and Beaston, and Wassermann's chorea streptococcus.

Pyogenic Staphylococci.[1]—This group includes a number of micrococci, some of which more than any other organism are ubiquitous. The **Micrococcus pyogenes aureus** occurs singly, in pairs, in fours, and in short chains, most commonly in irregular masses. It is a non-motile, facultative anaerobe, measures 0.8 μ to 1 μ, and grows readily on all laboratory media at temperatures between 20° C. and 40° C., the optimum being 30° C. to 37° C.; it is killed by exposure for half an hour at 80° C. In gelatin the growth is rapid and the medium liquefied; a faint white streak appears along the line of puncture, the growth gradually, by the third day, assuming a deep yellow or golden hue. The organisms fall to the bottom of the liquefied medium, forming a deep yellow sediment. Stroke cultures on agar develop as thin, white, slightly yellowish, opaque films, irregular in outline. The characteristic yellow color appears by the third day. The agar frequently becomes cloudy and opaque, but does not liquefy. In virulent cultures, solidified blood serum is liquefied. On potato the culture is white, later taking on a yellow color, and with age becoming succulent and yielding a sour odor. On plates the growth appears within twenty-four to thirty-six hours, as slightly elevated white colonies with sharply defined edges; gradually the golden-yellow color develops. It renders bouillon turbid, depositing as a brownish-yellow sediment. It stains by the usual anilin dyes and by Gram's method.

FIG. 64.—MICROCOCCUS. (STAPHYLOCOCCUS) PYOGENES AUREUS. —(*Coplin and Bevan.*) ×800 diameters.

The **Micrococcus pyogenes citreus** in every respect resembles the aureus except that it develops a lemon yellow color. The **Micrococcus pyogenes albus** has essentially the same characteristics except that its growth is slower and the colonies are milk white in color. The **Staphylococcus epidermidis albus** is probably a strain of the preceding organism. The **Micrococcus cereus albus** is slightly larger, the colonies are small and white, wax-like, and it does not liquefy gelatin. The **Micrococcus cereus flavus** is a similar organism except that it develops a yellow pigment.

The pyogenic or pus-producing staphylococci stain by practically all of the laboratory methods and are positive to Gram. The Micrococcus pyogenes aureus is the organism most commonly found in suppurative processes. Curry[2] found it in 52 of 115 abscesses; the albus

[1] The term staphylococcus is much used, particularly by surgeons, instead of micrococcus. The student should remember that the terms are interchangeable. For references see page 81.

[2] "Medical and Surgical Reports of the Boston City Hospital," 1897.

was present in 29. The aureus was the only organism present in 32. The fact that this organism is constantly present on the surface of the body and on the mucous membranes accounts for the frequency with which it is found in surgical infections. The pathogenicity of the different members of the group varies, nor is it always the same for any one of the staphylococci. It has been demonstrated that there are saprophytic staphylococci, and it is probable that these are attenuated forms of the pathogenic. Neisser and Vechsberg have shown that pathogenic staphylococci produce *hemolysins* and *leukocidins*, while the saprophytic do not. Klopstock and Bockenheimer have found that animals immunized to pathogenic staphylococci produce sera agglutinating these organisms but not the saprophytic form.

The most characteristic features of the staphylococci are their intense positive chemiotactic action on leukocytes, particularly the polymorphonuclear. Cultures of the aureus sterilized by boiling may, when introduced subcutaneously, cause abscesses; if heated to 120° C. in the autoclave, this property is lost. Christmas has been able to isolate from filtered bouillon cultures a pyogenous substance to which he attributes the pus-producing faculty of the aureus. Introduced into the circulation in sufficient numbers the pyogenic staphylococci may give rise to septicemia or pyemia. There is abundant evidence to show that in animals, and probably in man, these bacteria are frequently present in the circulating fluid; ordinarily the number is small and conditions are unfavorable for colonization. The occurrence of an injury, which may be trifling in extent, develops a point of lessened resistance in which the organism may develop. In addition to the ordinary suppurative lesions caused by staphylococci, they may be found in osteomyelitis, endocarditis, cellulitis, in the pustules of acne and smallpox, and in the throat lesions of scarlet fever and diphtheria. When present as concurrent infections, absorption of the products of the pyogenic organism intensifies the lesions and symptoms due to the disease with which they are associated.

The **Streptococcus pyogenes**[1] (Rosenbach, 1884) is a non-motile, aerobic, pus-producing, chain-forming coccus, 0.4 μ to 1 μ in diameter; its optimum temperature is 35° C. to 37° C. It does not grow well below 25° C. to 30° C. and is extremely susceptible to even slight elevations, being killed in ten minutes at 52° C. On gelatin plates it gives rise to small, circular, finely granular colonies, which when fully devel-

[1] See foot-note, p. 81. Discussion before the Med. Soc. of London, Jan. 11, 1904. Ruediger, "Jour. Amer. Med. Assoc.," Oct. 17, 1903, "The Production and Nature of Streptocolysins," with bibliography; also "Jour. Amer. Med. Assoc.," Jan. 21, 1905, "Mechanism of Streptococcus Infection." Petruschky, "Zeit. f. Hyg. u. Infek.," xxiii, No. 1, "Nonspecific Character of the Erysipelas Streptococcus." Bulloch, "Trans. of Brit. Inst. of Preventive Med.," 1st series. Bergey, "Penna. Med. Jour.," Nov., 1903, p. 71, "Streptococci and Antistreptococci Sera"; bibliography. Weaver, "Jour. of Med. Research," May, 1903, "Streptococci, Especially in Scarlatina"; also "Trans. Chicago Path. Soc.," Feb. 9, 1903. Hektoen, "Jour. Amer. Med. Assoc.," March 14, 1903, on "Streptococcemia in Scarlet Fever." De Wale and Sugg, "Arch. Intern. Pharmacodyn. et Therap.," vol. 12, fasc. 3 and 4, 1903, p. 205, "Streptococcus in Variola." Zelenski, "Wien. klin. Woch.," April 14, 1904, "Agglutination of Streptococci." Schamberg and Gildersleeve, "Medicine," Sept., 1904, "Streptococci and other Organisms in the Throat in Scarlet Fever." The principal facts with regard to agglutination of streptococci may be obtained from Weaver,

oped are light brown, often extending from the margins irregular, serpentine filaments; gelatin not liquefied. On bouillon some streptococci grow much better than others. One strain of the organism may produce cloudiness without film or sediment, others give rise to a pellicle which, after formation, settles to the bottom. Most streptococci form acids. On agar small, whitish, slightly elevated colonies 1 mm. to 2 mm. in diameter develop; they may become confluent. The streptococcus frequently coagulates milk, sometimes rapidly, often slowly, and occasionally not at all.

Demonstration.—The streptococci stain readily with most anilin dyes. The different cocci in the same chain do not all stain with the same intensity nor are they all the same size. It is practically always Gram-positive; Étienne has obtained from the false membranes in angina a streptococcus that does not take the Gram stain, and Lemoine has found a similar organism in erysipelas; the reaction to Gram may be modified by cultivation. Vandevella studied twenty strains of streptococci, many of which were dissimilar, although he regarded them as being members of the same group. Foulerton investigated twenty-five strains and believes there is more than one distinct species.

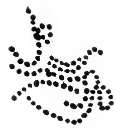


Fig. 65.—Streptococcus of Erysipelas.—(*Coplin and Bevan.*) × 800 diameters.

Pathogenesis.—The virulence of streptococci varies widely. It may be increased by passage through animals and diminished by cultivation. Cultures preserved under conditions that exclude oxygen retain their virulence. Various cytolytic poisons are produced by the streptococcus; the most important of these attack the red blood-cells (erythrocidins) and leukocytes (leukocidins). Sterile cultures may contain poisons sufficiently active to kill small animals, and it seems reasonable to conclude that the symptoms of streptococcus infection in man are due to the intracellular and extracellular toxins produced by the organism The serum of animals immunized to the streptococcus contains, among other substances, agglutinins which may be utilized for identifying the organism.

Streptococci have been found in a large number of morbid processes, among which especially should be mentioned suppurative lesions, erysipelas, peritonitis, pericarditis, pleurisy, meningitis, and arthritis;

"Jour. of Infectious Diseases," 1904, vol. iv, p. 91. Cole, "Jour. of Infectious Disease," Nov. 5, 1904, p. 714, "Experimental Streptococcus Arthritis and its Relation to Acute Rheumatism." Foulerton, "Lancet," Dec. 31, 1904, p. 1828. Hiss, "Jour. of Exper. Med.," vol. vi, p. 317, "Differentiation of Pneumococcus and Streptococcus." Simon, "Centralbl. f. Bakt.," 1903, xxiv, also Vaughan, "The Physician and Surgeon," May, 1904, "The Streptococcus Toxin." Schlie-singer, "Zeit. f. Hyg. u. Infectk.," 1903, Bd. xliv, p. 428, "Streptococcus hemolysins." Neumann, "Centralbl. f. Bakt.," xxxvii, 1904, p. 381, "Encapsulated Pathogenic Streptococci." Fischer, Ibid., p. 449, "Agglutination of Pathogenic and Saprophytic Streptococci." Discussion on Antistreptococcic Serum Therapy before the Berlin Med. Society, Feb. 8 and 15, 1905, reported in March number of the "Berl. klin. Woch.," also "La Semaine Méd.," March 1, 1905. Tunnicliff, "Trans. Chicago Path. Soc.," vol. vi, "Streptococci on Normal Tonsils." With regard to treatment by antistreptococcic serum consult the following: Ayer, "Med. Record," March 4, 1905. Hamilton, "Amer. Jour. of Obstet.," Nov., 1904. Peham, "Arch. f. Gynek.," Bd. lxxiv, p. 47.

certain strains of the organism produce a highly virulent puerperal fever. The **streptococcus erysipelatis** (Fehleisen) possesses no constant characteristics by which it may be differentiated from some strains of pyogenic streptococci, and it has been shown by a number of observers that, using the same chain-forming coccus, cuticular inoculation gives rise to erysipelas and subcutaneous injection causes abscess formation.

The relation of streptococci to scarlet fever has been studied recently by a number of observers, the consensus of opinion being that it is not the cause of the disease. The lowered vital resistance of patients having scarlet fever and diphtheria favors colonization of pathogenic streptococci primarily in the pharyngeal lesions, from which the poisons produced by the organism may be absorbed, or the germ, entering the circulation, may further embarrass the already heavily taxed protective powers of the patient, causing a fatal issue. Whether the poisons of the streptococcus be absorbed from a local lesion or produced in the circulating blood (streptococcemia), they exert a powerful action on the tissues. Degenerative or necrotic changes occur in the muscles, particularly the heart, and also in glandular viscera, especially the liver and kidneys. The spleen enlarges and contains areas of necrosis; proliferative activity is manifested by the bone-marrow, in which necrotic processes may also develop. Degenerative, or rather toxic, manifestations have been noted in the central nervous system. Should the streptococcus colonize, abscess formation (streptococcic pyemia) occurs. A highly virulent type of endocarditis is sometimes produced by this organism.[1] Localized on the intima of the arteries or veins the streptococcus produces septic thromboarteritis or thrombophlebitis, which may extend for a considerable distance along the course of the affected vessel; in this way the thrombosing phlebitis and lymphangitis (milk leg) of puerperal sepsis may be produced. The studies of Hasenknopf and Salge[2] and Neufeld[3] indicate that while agglutination tests may be of value in the identification of streptococcal infections, the variability of sera and the agglutinability of various strains of streptococci render it difficult to estimate in any given case the trustworthiness of the results obtained. The sera of animals immunized to the streptococcus have been used in the treatment of streptococcal infections; it has been established that such sera possess protective powers and may be of value. Serum obtained from an animal immunized against a single strain of streptococci (monovalent serum) is very much less efficacious than that obtained from animals immunized to a number of strains (polyvalent serum); the latter has been found useful in such streptococcic infections as erysipelas and streptococcemia, especially that occurring in puerperal sepsis. It is probable that the usefulness of these sera depends, in part at least, on the presence of antistreptocolysins.

The **Micrococcus melitensis**[4] (Bruce, 1887) is a round or slightly oval coccus, about 0.33 μ to 0.5 μ in diameter, sometimes arranged as

[1] See Endocarditis in chapter on Diseases of the Vascular System.

[2] "Jahrb. f. Kinderheilk.," 1903, vol. lviii.

[3] "Zeit. f. Hyg.," 1903, vol. xliv.

[4] See works referred to in foot-note, page 81. Sandwith, "Practitioner," June, 1904, p. 791. Carbone, "Arch. di scienze med.," 1904, 2e fasc., p. 273 Allen, "Jour. of Royal Army Med. Corps," 1904, p. 699; the latter volume contains a number of references to this organism. Allbutt's "System of Medicine," vol. ii, p. 463.

diplococci, rarely forming short chains, and usually thought to be non-motile; with regard to the motility authorities are not agreed. In cultures occasionally one diameter of some of the organisms increases, giving rise to bacillary forms. It slowly clouds bouillon, eventually forming a deposit but no surface film. Agar containing 0.5 per cent. peptone is the best medium; stroke cultures on the surface give rise to small, whitish, slowly enlarging colonies 2 mm. to 3 mm. in diameter and more opaque at the center than at the periphery, which may be serrated. There is a slowly developing, scanty growth on gelatin, but the medium is not liquefied.

Demonstration.—The organism is obtained in culture by inoculations made from the spleen. It stains with the usual anilin dyes, but is Gram-negative; neither films nor spreads bear alcohol differentiation.

Pathogenesis.—The disease produced in man by the Micrococcus melitensis is called **Malta fever.** The ordinary laboratory animals are refractory, but the affection has been produced in monkeys, in which it runs a typical course. In man the spleen is greatly enlarged, soft and friable; the incised surface is dark, intensely congested, and the sinuses enormously distended with blood. The organism can readily be demonstrated in the softened splenic pulp. The liver is swollen, dark in color, with more or less conspicuous interlobular round-cell infiltration. The kidneys are congested, the capsules easily detached, and there may be subcapsular and interstitial hemorrhages. The large intestine is often congested and the mesenteric glands may be slightly enlarged. Ulcerations do not occur. The disease is of variable duration, sometimes lasting several weeks; Bruce states that the mortality is about two per cent. It has generally been thought that infection occurs by the alimentary canal. Allen thinks it will eventually be shown that Malta fever is disseminated by some insect.

Agglutination may be of some value in diagnosis, although the dilution necessary may be anywhere between 1 in 10 and 1 in 1000.[1]

The **Micrococcus tetragenus**[2] is a non-motile, facultative anaerobe, 0.6 μ to 1 μ in diameter, occasionally found in groups of two, usually four, and, in the body fluids and tissues, often appears encapsulated. On gelatin plates it gives rise to small, white, finely granular colonies having a vitreous luster; it grows well on agar, potato, and blood-serum, forming a heavy white surface colony. The growth is at first slow, but after from forty-eight to seventy-two hours more rapid. Does not liquefy gelatin.

Demonstration.—The tetracoccus stains by the usual anilin dyes and by Gram's method.

Pathogenesis.—It may be made to infect mice and guinea-pigs, but in man it appears to be largely a saprophyte. It has been found alone in abscesses, particularly around the teeth. Usually it is encountered in sputum and tuberculous cavities and has been observed with the pneumococcus in the pus of empyema and meningitis. A tetracoccemia can be produced in animals, but it is doubtful if the organism ever so affects man.

[1] For method of agglutination, see chapter on Bacteriologic Technic.
[2] See works referred to in foot-note, p. 81.

The **Bacillus diphtheriæ**[1] (Klebs, 1883; Löffler, 1884) is a straight or slightly curved rod, extremely pleomorphous, measuring 2 μ to 4.8 μ in length and 0.3 μ to 1 μ in breadth; branched, granular, barred, and other irregular forms occur. The organism is a non-motile aerobe and facultative anaerobe, optimum temperature 37° C., minimum 18° C., and does not grow above 42° C. Vitality may be preserved for about a year. It grows best on Löffler's blood-serum mixture, on which colonies are visible in twenty-four hours, as small, grayish, opaque dotlets, easily extended by any overflowing water of condensation. In gelatin stab cultures, small whitish or grayish-white dots develop along the needle track, while on the surface the puncture is surrounded by a growth somewhat thicker in the middle; the medium does not liquefy. Growth on agar resembles that on serum; the growth on potato is at first invisible and may develop a thin, grayish glaze. Spore formation is not believed to occur. Grown in bouillon containing glucose the medium at first becomes acid and later alkaline in reaction.

Demonstration.—Swabs are prepared by firmly wrapping one end of a piece of wire (fourteen centimeters long and about two millimeters in thickness) with cotton, which should completely cover the end, so as to prevent possible injury when the swab is applied. Ten centimeters from the same end a second roll of cotton is placed around the wire, sufficiently large to fit tightly into the mouth of a test-tube. The swab and test-tube are sterilized in a hot-air sterilizer. The inoculations are obtained by rubbing this swab over the affected area and then at once gently smearing the surface of a slant tube of Löffler's

[1] See works referred to in foot-note on p. 81. For recent literature on the toxins see Ehrlich, "Berl. klin. Woch.," 1903; Calcar, "Berl. klin. Woch.," Sept. 26, 1904, p. 1028; Arrhenius and Madsen, "Centralbl. f. Bakt.," 1904, vol. xxxvi; Schwoner, "Centralbl. f. Bakt.," Bd. 35; Simon, "Arch. de Med. Exp. et d'Anat. Path.," Nov., 1903, p. 763; Rist, "Sôc. de Biol.," July 11, 1903; Pick and Schwoner, "Wien. klin. Woch.," Oct., 1904, p. 1065; Theobald Smith, "Jour. of Med. Research," vol. xiii, No. 3, p. 341. For recent studies on the toxic action of the diphtheria bacillus see Rist, "Rev. mens. de l'Enfance," Sept., 1904, the "Pathogenesis of Diphtheritic Paralysis." Rolleston, "Practitioner," Nov., 1904, p. 597, "Clinical Observations on Diphtheritic Paralysis." Babonneux, Thesè de Med. Paris, 1904, "Experimental Diphtheritic Paralysis." Bolton, "Lancet," Feb. 4, 1905, p. 278, "Diphtheritic Toxemia." Hayem, "Soc. Méd. des Hôp.," Feb., 1905, "Gastric Lesions Produced by Diphtheria Toxin." Graham-Smith, "Jour. of Hyg.," 1904, "Virulence of Diphtheria Bacilli," exhaustive study with bibliography. Spirig, "Zeit f. Hyg.," vol. 42, p. 420, careful study of bacillus. Klein, "Centralbl. f. Bakt.," vol. xxxiii, p. 488, a new member of the diphtheria group. Laird, "Albany Med. Annals," May, 1903, p. 352; "Pediatrics," Sept., 1903, p. 532, "Different Forms of Diphtheria Bacilli." Newman ("The Practitioner," Nov., 1903), very full review of the bacteriologic diagnosis of diphtheria. The bibliography is given to date. Abbott and Gildersleeve, "Centralbl. f. Bakt.," Dec. 18, 1903, p. 273, "Branching Forms of the Bacillus." Andrade, "Med. News," Dec, 3, 1904, p. 268, review of groups. Concetti, "Ann. d'Igiene sper.," vol. xi, "Actinomyces Forms of the Diphtheria Bacillus." Blumenthal and Lipskerow, "Centralbl. f. Bakt.," March 11, 1905, "Differential Staining Methods." Knapp, "Jour. of Med. Research," Nov., 1904, "Identification of the Bacillus." Hamilton, "Jour. of Infect. Diseases," vol. i, 1904, "Virulence of So-called Pseudodiphtheria Bacilli." See also Nothnagel's "Encyclopedia of Practice of Medicine," American edition, "Diphtheria, Measles, Scarlet Fever, Rötheln." Royer, "Proceed. County Med. Soc.," Feb. 28, 1904, "Antitoxin Treatment." "Public Health," June 8, 1903, discussion of methods of dissemination.

medium. Spreads may also be made from the swab on cover-glasses and may be fixed in the usual manner. Colonies on Löffler's medium appear within twenty-four hours. They are grayish in color, moist, round or oval in outline, slightly more elevated and opaque at the center. Spreads from such colonies, stained with Löffler's methylene-blue, will show the organism as previously described; also as club-shaped and irregular rods. These so-called involution forms, staining irregularly, are of great diagnostic value, although not pathognomonic. Sometimes examination of spreads from the moist swab yields data corroborative of the clinical diagnosis; if the cotton is moistened with sterile glucose bouillon and the swab and test-tube incubated, bacilli may be found in demonstrable numbers before the serum culture is productive. Ohlmacher found that bacilli may be demonstrable on the medium some hours before colonies are visible macroscopically. He recommends that after four hours' incubation spreads be made and stained by the usual methods. Invisible growths may be present after eighteen hours at room-temperature.

Neisser's Differentiating Stain.—Dissolve 0.5 gm. of methylene-blue (Grübler) in 10 c.c. of commercial alcohol; add to this 425 c.c. of distilled water and 25 c.c. of glacial acetic acid; stain cover-glass preparations for from two to three minutes; wash in water, and stain for five seconds in solution made by dissolving 0.5 gm. of vesuvin in 250 c.c. of boiling distilled water; wash in water, dry, and mount. This method shows to advantage the polar granules (metachromatic granules) in the diphtheria bacillus; organisms without polar granules are not those of diphtheria. Pseudodiphtheria bacilli may, rarely, show polar granules.

The pathogenicity of the organism may be tested by subcutaneous injection of 0.5 c.c. of bouillon culture from twenty-four to forty-eight hours old. This should kill a medium-sized guinea-pig.

Pathogenesis.—The virulence of the organism varies within wide limits, is rarely the same for any two cultures, and is most marked in young growths; during cultivation it is lost more quickly on agar than on serum or in bouillon. Occasionally attenuated and non-virulent forms can be made to reacquire virulence. Roux and Yersin have shown that the non-virulent organism is rendered more active by concurrent infection with the streptococcus—an association frequently observed in diphtheria. Inoculated on the mucous membrane, catarrhal, pseudomembranous, or gangrenous inflammation ensues, with more or less systemic intoxication. The local lesions vary widely in extent, and are sometimes acute and fulminating; Neufeld[1] states that the chronic may follow the acute or that a local lesion may be chronic from the beginning and can persist for months or even years. The bacillus may be present during long periods.

The organism enters the blood in a considerable percentage of cases. It is frequently found in the lungs postmortem, and may be the only organism present in the associated pneumonia. It has been found in endocarditis and may be excreted in the urine. The surface lesions of diphtheria usually occur in the throat or nose; in the larynx (laryngeal diphtheria) pseudomembrane formation may occlude the passage. Diphtheria of the esophagus and stomach is rare; the con-

[1] "Deut. med. Woch.," May 12, 1904.

junctiva, external genitals, and anal margin may be attacked. Blistered surfaces are sometimes infected by the diphtheria bacillus.

Clinical and experimental studies clearly establish that the diphtheria bacillus produces all its manifestations through the activity of the poisons which it elaborates. Often death appears to be due to the toxemia alone. Recent studies seem to indicate that in order to explain the clinical and pathologic phenomena of diphtheria it is necessary to recognize at least three toxic elements. The most active of these is the extracellular poison, easily obtained from cultures, and to the action of which must be attributed granular and fatty changes in the muscles, particularly of the heart, and the degenerative and necrotic lesions affecting the other viscera, especially the liver, spleen, and kidneys. In the liver more or less cloudy swelling and multiple areas of coagulation necrosis may be found. The renal lesions differ widely, and in the severer forms may in part be due to concurrent streptococcal infection. In the milder cases there is considerable granular change in the tubular epithelium, which may undergo necrosis and be cast off. An acute diffuse nephritis is not infrequently present, especially in fatal cases; with associated streptococcus infection minute abscesses (acute suppurative nephritis) may be found. The spleen is enlarged, the pulp soft and friable, there is more or less endothelial proliferation and evidences of hemolysis; areas of focal necrosis are practically always present.

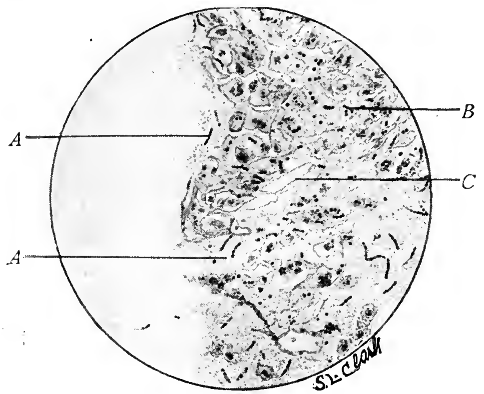


FIG. 66.—MARGIN OF MEMBRANE FROM TONSIL, CASE OF DIPHTHERIA.

A A. Diphtheria bacilli; the pointer from the lower *A* ends in an area of granular material. *B* Cocci. *C*, Strands of fibrin. The cellular elements present are squamous epithelium, and polymorphonuclear and hyaline leukocytes.

Welch and Flexner have shown that the local lesions of diphtheria are probably due to an intracellular toxin (endotoxin). Schwoner has demonstrated that the diphtheria bacillus produces a hemolytic toxin (diphtheriolysin) which acts principally on the red blood-cells. Babonneux, in animals, has succeeded in producing a localized paralysis restricted to the region of the inoculation, not generalizing, often ending in recovery, and in other ways resembling the diphtheritic paralysis occurring late in, or coming on after, diphtheria of man. Rolleston, Bolton, and others are of the opinion that the diphtheritic paralysis in man is due to some endotoxin. The fact that the antitoxin treatment of diphtheria has greatly reduced the mortality, but not to the same degree influenced the occurrence of paralysis, speaks in favor of this view. It is argued that the prevailing method of inducing immunity in horses, by the use of filtered cultures, affords an antitoxin for the extracellular poisons but offers no protection from the intracellu-

lar toxin (endotoxin). It is also possible that the diphtheritic paralysis may be due to some poison resembling or related to the toxone described by Ehrlich. Bolton particularly adheres to the belief that affections of the peripheral nerves are due to the action of a toxone.

Diphtheria Antitoxin.[1]—The antitoxic treatment of diphtheria is one of the most brilliant achievements that has followed the laboratory study of disease. Repeated administration of diphtheria toxin gives rise to powerful antitoxic bodies which are contained in the circulating blood of the animal treated and may be obtained from the serum in a form suitable for administration. The antitoxin, if administered sufficiently early in an attack of diphtheria, fully neutralizes the poisons produced by the bacillus. In order to be successful the treatment must be inaugurated early—the earlier the better—and the agent must be administered in a sufficient quantity.

Diphtheria antitoxin may also be used for immunizing individuals exposed to infection by the bacillus. The introduction of an adequate amount of antitoxin anticipates infection and protects against the toxin which would otherwise exert a deleterious action on the tissues of the body even before symptoms became manifest.

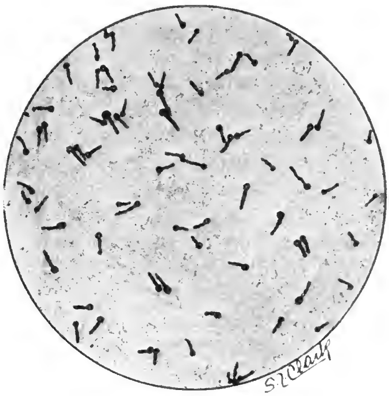


FIG. 67.—BACILLUS TETANI. PURE CULTURE FROM WOUND.

Tetanus is a specific infection due to the **Bacillus tetani**[2] (Nicolaier). The organism is 3 μ to 5 μ long, 0.3 μ to 0.7 μ thick, motile (except in the spore stage), flagellated, and develops involution forms; drumstick ends are seen on many of the bacilli and are evidences of spore formation. The spore is almost always at one end. Under ordinary conditions the bacillus is a strict anaerobe, but may, by prolonged cultivation, be made to grow in the presence of air. It liquefies gelatin and is feebly gas-producing. Deep stab cultures in gelatin develop first as a faint cloud from which lateral projections are formed; liquefaction proceeds slowly, gas bubbles appear, and the organism gradually forms a deposit on the bottom of the tube. It does not liquefy solidified serum. In bouillon, excluded from oxygen, development is rapid, the medium becomes cloudy, fine gas bubbles appear, and eventually the organisms are precipitated. Cultures give off a faint odor resembling

[1] For the preparation of antitoxin see chapter on Bacteriologic Technic.

[2] See references in foot-note on p. 81. Moschocowitz, "Annals of Surgery," 1900, vol. xxxii; Elting, "Albany Med. Annals," Jan., 1904; Vincent, "Annales de l'Inst. Pasteur," July 25, 1904, p. 450. Holbeck, "Deut. med. Woch.," March 5, 1903. Creite, "Centralbl. f. Bakt.," Oct. 17, 1904, p. 312. Sachs, "Berl. klin. Woch.," 1904, No. 16. Zupnik, "Wien. klin. Woch.," Jan. 23, 1902. Demontmerot, Thèse de Paris, 1904, No. 471. Marinesco, "C. R. Soc. de Biol.," 1904, vol. 57, p. 62. Tiberti, "Centralbl. f. Bakt.," 1905, Bd. xxxviii, p. 281. Meyer and Ransom, "Arch. f. exper. Path. u. Pharmacol.," 1904, Bd. xlix. Richardson, "Boston Med. and Surg. Jour.," April 7, 1904, p. 493.

that of burning horn. In bouillon the reaction becomes clearly alkaline; milk is rendered amphoteric without coagulation. The organism does not grow below 14° C., develops poorly at 18° C., the optimum temperature is 37° C., although cultures may be obtained at 42° C. Spores resist six hours' exposure to 80° C., but are killed by steaming for one hour. Their resistance to chemic disinfection is also great. Miquel has shown that in earth they may live sixteen years.

Demonstration.—The organism may be stained with any of the basic anilin dyes and is Gram-positive; the spore is more resistant and often stains at the periphery only. The tetanus bacillus is difficult to obtain in culture; the best results are secured by making anaerobic cultures which, when fully developed and containing drumstick organisms, are exposed to a temperature of 80° C. for forty-five minutes; this treatment usually destroys the associated bacteria. Richardson recommends cultivation in blood-serum at 37° C. for several days, using tissue or pus from the wound. The growth of symbiotic organisms consumes the oxygen and permits the tetanus bacillus to develop. The resulting semifluid offensive mass is then subjected to heating and anaerobic cultures are made. The presence of drumstick bacilli indicates that the culture contains the tetanus or pseudotetanus bacillus described by Bain.[1] The latter organism is Gram-negative, non-pathogenic for guinea-pigs; does not liquefy gelatin or glucose-gelatin, and glucose-agar cultures are unlike the true tetanus bacillus.

Pathogenesis.—The tetanus bacillus usually infects man and horses, although mice, white rats, and guinea-pigs are susceptible. In the tissues the growth of the organism is usually restricted to the point of inoculation. According to Holbeck, there are four cases on record in which the bacillus has been found in the blood; Creite has isolated it from the lungs. Manifestations due to the bacillus are brought about entirely through the action of its powerful toxins, of which Prieger found that 0.000005 gm. would kill a mouse. According to Kupnik, tetanus toxin exerts a local action on the muscles or the nerve-endings in the muscle, but all observers agree that its chief manifestation is brought about by its influence on the motor cells of the spinal cord. Wassermann showed that tetanus toxin became firmly attached to nerve tissues; in discussing the problems of immunity I have already referred to this fact. Recent studies by a number of investigators indicate that the poison reaches the nerve-centers by passage along the larger trunks rather than by the general circulation, as previously believed; this fact offers an explanation for the occasional occurrence of symptoms beginning in the muscles near the point of infection. In addition to its action on the nervous elements it has been shown that the bacillus produces a hemolytic poison.

Postmortem, areas of hyperemia may be found in the spinal cord; under the microscope points of hemorrhage are sometimes found with moderate alteration in the nuclei (karyolysis) and conspicuous changes in the Nissl bodies (tigrolysis) of the motor cells. Marinesco has shown that important alterations in the neurofibrils are also present, and Odier has demonstrated degenerative changes in the nerves. The alterations found in the muscles are the result of the spasm and not due directly to the action of the tetanus poison. They consist in microscopic or

[1] "Jour. of the Boston Soc. of the Med. Sciences," 1901, vol. v, p. 506.

macroscopic hemorrhages and occasionally fragmentation of the muscle fibers or even gross tears.

Tetanus Antitoxin.—Tetanus is probably the best known example of a disease produced by a toxic microorganism; for this reason much was hoped for the antitoxin treatment of the affection. An effective antitoxin can readily be obtained from immunized animals, and it is easily established that it efficiently neutralizes the poison produced by the bacillus. Its administration, however, in cases of tetanus, has been disappointing. This well-recognized clinical result may depend upon the toxin having become firmly anchored to tissues before symptoms manifest themselves, the antitoxin being administered too late to prevent irreparable damage. Recognizing that the toxin acts intensely upon the central nervous system, subdural injection of the antitoxin has been practised, but even when administered in this manner, its influence on the disease falls far short of our expectations. The best use to which the antitoxin has been put is for the purpose of immunizing individuals in whom infected wounds, likely to give rise to tetanus, have been received.

Meat Poisoning.—The consumption of meat in which bacterial decomposition has led to the production of toxic substances gives rise to a variety of intoxications, among which should be mentioned **botulism,** due to a toxin produced by the **Bacillus botulinus.**[1] The germ is 4 μ to 6 μ in length and 0.9 μ to 1.2 μ in thickness, strictly anaerobic, flagellated, slightly motile, growing as low as 16° C. and up to 40° C., with an optimum temperature between 25° C. and 30° C. The spores are killed by exposure to 80° C. for one hour. It liquefies gelatin with the evolution of gas, produces acids, among which may be mentioned butyric acid, but does not coagulate milk.

Demonstration.—The Bacillus botulinus stains by the usual methods, and may, with care in differentiation, be tinged by the method of Gram. The flagella are difficult to stain. Cultures may readily be obtained by the usual anaerobic methods.

Pathogenesis.—The organism does not grow readily in the living tissues of man or lower animals, but exerts its disease-producing quality by means of poisons of extreme activity. Growing in pork, sausage, or other meat, the elaborated poisons are retained in the food and manifest their deleterious action after the food is taken. The studies of Marinesco, Kempner and Pollack, and also Pollack and Brieger, have shown that the toxin affects particularly the central nervous system, the ganglion cells of which may be the seat of marked chromatolysis. Animals may be immunized to the action of the poison, and an *antibotulin* has been suggested for treating the intoxication produced by the germ poison.

Anthrax,[2] Malignant Pustule, Mycosis intestinalis, Anthracemia,

[1] See works referred to in foot-note on p. 81.

[2] See works referred to in foot-note, p. 81. Scagliosi, "Centralbl. f. Bakt.," 1904, Bd. xxxvii. Pruszynski, "Gaz. lekarska," Nov. 12, 1904. Skezely, "Zeit. f. Hyg.," xliv, 1903. Jopson and Ghriskey, "Proc. Path. Soc. of Phila.," Jan., 1900. Gilruth, "Lancet," Feb. 4, 1905. Heim, "Münch. med. Woch.," March 8, 1904. Preisz, "Centralbl. f. Bakt.," 1904, Bd. xxxv. Schottmüller, "Münch. med. Woch.," Sept. 27, 1898. Legge, "Milroy Lectures on Industrial Anthrax," "Lancet," 1905, vol. i. Bail and Petterson, "Centralbl. f. Bakt.," vol. xxxiv–xxxvi; see also Vaughan's article on "Cellular Toxins," "Jour. Amer. Med. Assoc.," March 28, 1903, p. 838.

and **Wool-sorter's Disease** (*Splenic Fever*, *Mal-de-rate*, *Milzbrand*) are names applied to the manifestations of an infectious disease affecting man and most vertebrate animals and due to the **Bacillus anthracis.** The organism is rod-shaped, spore-forming, non-motile, and grows at temperatures between 12° C. and 45° C., the optimum being 37° C. The spore-free bacillus is killed at about 60° C. (moist heat); the spores require boiling for at least sixty minutes. In breadth the bacilli measure from 1 μ to 1.5 μ; in length the typical rod is 4 μ to 8 μ, but long continuous chains often occur. In agar or gelatin plates the growth appears as a small, white dotlet which later develops hair-like projections from the periphery, and in gelatin liquefies the medium. In bouillon threads and occasionally flocculi are formed which later precipitate. Stab cultures in gelatin show the characteristic inverted fir-tree growth consisting of a dense stem along the track of the needle with innumerable lateral projections; later liquefaction occurs. The organism coagulates and peptonizes milk with the evolution of acid.

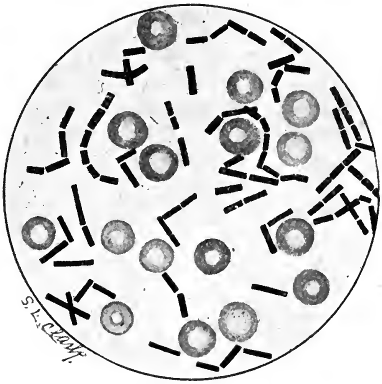


Fig. 68.—Bacillus anthracis in Blood of Rabbit.

With regard to the **toxin** production we are indifferently informed. Various substances have been isolated from the cultures and from the organism; some of these are toxic. Vaughan has established the presence of an intracellular toxin, and the studies of Martin indicate that the poison producing the local symptoms is different from that causing the fever and other systemic phenomena; discussions as to the exact chemistry of the poisons elaborated by the bacillus have not been illuminating.

Attenuation.—Pasteur found that by cultivation at 43° C. the organism became less virulent and ceased to form spores; after twenty-four days it failed to transmit the disease in susceptible animals, which later withstood inoculation with bacilli grown at the same temperature (42° C.) for twelve days; animals receiving both these vaccinations became immune to virulent bacilli, although the insusceptibility was of relatively short duration, not exceeding one year. Sobernheim[1] immunizes by the simultaneous administration of 5 c.c. of anti-anthrax serum and 0.25 to 0.5 c.c. of culture. Anti-sera have been prepared by Sclavo, Sobernheim, Mendez and others. Sclavo obtains his serum from immunized sheep, and uses it not only for producing insusceptibility but for the treatment of anthrax in man; the mortality from anthrax in the whole of Italy is twenty-four per cent.; of the cases treated by Sclavo's serum, six per cent. died.

Demonstration.—From a case of suspected anthrax cultures should be made, a guinea-pig or mouse inoculated with the suspected material, and spreads from the blood and diseased tissue stained with the usual dyes and by Gram's method. Frequently the films contain

[1] "Deut. med. Woch.," 1904, Nos. 26 and 27.

demonstrable numbers of Gram-positive rods with squarely-cut ends. By the time characteristic cultures have been obtained the inoculated animal will probably have died and the demonstration of the organism in its blood is quite conclusive. Blood cultures from a patient are of both diagnostic and prognostic value.

Pathogenesis.—In man several closely related forms of anthrax occur; infection is usually brought about by handling hides, carcasses, hair, or wool derived from infected animals. It is possible to recognize three paths of infection,—cutaneous, intestinal, and pulmonary,—and possibly to these should be added an occasional instance of blood infection in which the point of entrance cannot be determined. It is possible that infection may occur by the bites of insects, and it is certain that minute, often unsuspected solution in the continuity of the surface epithelium may permit entrance of the organism. A number of cases of transplacental infection are on record.

Cutaneous anthrax, in over ninety per cent. of the cases, begins on the arm, face, or neck. There is rarely more than one primary lesion, although four have been observed in a single case. The affection begins as a red papule, rapidly develops into a vesicle, which, as it enlarges, is attended by the formation of a red brawny induration at the base and later a necrotic area appears in the center. In severe forms the edema is most marked, and in some cases the intense redness merits the term **erysipelatous anthrax,** occasionally applied. The edema may be extensive; the nearest lymph-nodes usually are enlarged.

When the bacillus enters by the alimentary canal **intestinal anthrax** (*Mycosis intestinalis*) is produced. The ileum and caput coli are principally affected; the mucous membrane of these structures is injected, and not infrequently is the seat of minute ulcers and diffuse submucous hemorrhages. This form is practically always fatal.

In **pulmonary anthrax,** blood infection (*anthracemia*) develops early. At autopsy the lungs are found edematous, often gelatinous; subpleural ecchymoses and effusions into the cavities, particularly the thoracic, are usually present. In most cases more or less bronchitis and some enlargement of the bronchial glands are present. The bacilli are found in large numbers in the bronchial mucosa, which also shows areas of hemorrhage; the contained mucus may be loaded with bacilli, which are also demonstrable in large numbers throughout the tissues.

No matter from what point infection occurs, when the bacillus enters the circulation widely distributed changes occur in the tissues. The muscles, including the heart, are darker than normal, and frequently contain minute hemorrhages; ecchymoses may also be found beneath the serous membranes; even the meninges and brain are affected. In man splenic enlargement is less constant than in lower animals. The organ is usually increased in size, dark in color, and the pulp diffluent. The bacilli may readily be cultivated from all the organs and are often present in enormous numbers.

The **bacillus of symptomatic anthrax**[1] is a motile, flagellated, anaerobic, spore-forming organism, 3 μ to 5 μ long, and 0.5 μ to 0.6 μ thick with rounded ends, occurring singly and in pairs. It liquefies gelatin, developing small, irregular spheres which later give off lateral spicules; the cultures yield an acrid, penetrating odor and the organism produces

[1] See works referred to in foot-note, page 81.

gas and acid. It rapidly coagulates milk. The optimum temperature is 37° C. to 40° C., the minimum 13° C. The organism is extremely resistant to heat, requiring at least one hour's boiling in order to assure its destruction.

Demonstration.—The bacillus stains by the common anilin dyes, and is usually Gram negative if subjected to prolonged staining and brief differentiation may be made to take Gram's stain. Pure cultures may be obtained in much the same manner as directed for tetanus (see page 122).

Pathogenesis.—The bacillus is the cause of symptomatic anthrax (black-leg or quarter evil), known to the French as "charbon symptomatique," and to the Germans as "Rauschbrand." Guinea-pigs are very susceptible; natural infection occurs in cattle, sheep, and rarely in goats. Cats, dogs, pigs, rabbits, chickens, and ducks are immune. It is not known to infect man.

Influenza[1] is an infectious disease due to the **Bacillus influenzæ,**[2] an extremely thin organism 0.2 μ to 0.5 μ in length; it is non-motile and aerobic; the optimum temperature is 36° C. to 38° C., and it ceases to grow below 28° C. and above 42° C.; the thermal death-point is about 60° C. For cultivation a medium containing hemoglobin is necessary; blood-serum does not serve, although blood-smeared agar or media containing blood may be used. On suitable solid media the organism develops in the form of numerous, small, transparent, colorless, homogeneous droplets which with age take on a yellowish or brownish hue, but do not become confluent. The vitality of the bacillus is low and re-inoculations must be made every third or fourth day.

FIG. 69.—BACILLUS OF SYMPTOMATIC ANTHRAX CONTAINING SPORES.—(*Coplin and Bevan.*) × 800 diameters.

Demonstration.—The Bacillus influenzæ stains by the ordinary anilin dyes but not by Gram's method. Carbol-fuchsin diluted with nine parts of water is especially recommended. In order to obtain cultures appropriate media are inoculated with nasal or bronchial mucus diluted with sterile water; a number of tubes should be prepared, as associated organisms frequently overgrow the bacillus.

Pathogenesis.—The bacillus of influenza is found in the bronchial and nasal mucus, rarely in the blood of infected individuals; in the mucus from the respiratory passages it can readily be demonstrated, and often persists long after clinical recovery. Fifteen cases of influenzal meningitis are recorded. It has also been found in otitis media, conjunctivitis, pleurisy, endocarditis, encephalitis, cholecystitis, pyelonephrosis, and arterial thrombosis. Inflammation of the mucosa produced by the bacillus is of the catarrhal form; the abundant mucus contains varying

[1] Recently clinicians have inclined to the view that the condition ordinarily called influenza is a syndrome which may be due to infection by the streptococcus, pneumococcus, and unidentified organisms. All are agreed that one form is due to the influenza bacillus. See discussion, Soc. Méd. des Hôp., March 10, 1905.

[2] Ghon and v. Preyss, "Centralbl. f. Bakt.," 1904, Bd. xxxv, p. 31, "Biology of the Bacillus." Ricciardi ("Giornale Internaz. d. Scienze Med.," April, 1904, "Vitality of the Bacillus." Didsbury, "Annals of Otology, Laryngology, and Rhinology," Dec., 1904, "Influenza Bacillus in Otitis Media." Wright, "Boston Med. and Surg. Jour.," April 27, 1905, "Influenza Bacillus in Pyelonephrosis." Jundell, "Jahrb. f. Kinderheilk.," 1904, Bd. 59, p. 772, " Influenza Bacillus in Meningitis." Heyrovsky, "Wien. klin. Woch.," June 9, 1904, p. 644, "Influenza Bacillus in Cholecystitis; references to its Presence in Other Conditions."

numbers of phagocytes in which the bacilli are often found. Influenzal pneumonia is of the catarrhal type and manifested by numerous small foci of consolidation. Such areas, examined histologically, consist of distended alveoli containing polymorphonuclear and hyaline cells and a viscid fluid giving a mucin reaction. The fact that in some cases the exudate is particularly rich in polymorphonuclear cells indicates that the bacillus possesses pyogenic powers. It has been found in pure culture in abscesses. The organism is frequently associated with other bacteria, and, as is well known, influenza is not an infrequent complication of a number of affections. The bacillus is sometimes associated with the pneumococcus in croupous pneumonia. The influenza germ is occasionally present in inflammations of other serosæ than the meninges, but is rarely alone.

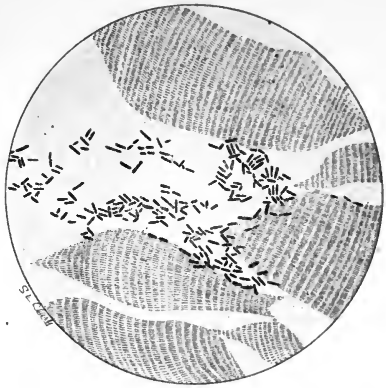


FIG. 70.—BACILLUS OF SYMPTOMATIC ANTHRAX BETWEEN MUSCLE-FIBERS OF INOCULATED GUINEA-PIG.

Of the **toxins** produced by the influenza bacillus accurate information is needed. That the symptomatology depends largely upon the influence of one or more poisons seems perfectly clear; in no other way is it possible to explain the symptoms, especially the profound depression, and such sequelæ as neuritis and myelitis, which sometimes follow the disease. It has not been possible to produce immunity in animals, and it is well known that in man one attack affords no protection and relapses are common.

The **Bacillus pneumoniæ**[1] (bacillus of Friedländer) is a pleomorphic organism slightly less than 1 μ in width and varying in length from 1 μ to 4 μ or 5 μ. It is aerobic, non-motile and in tissues and secretions, encapsulated. The optimum temperature is 37° C., the minimum 14° C., the maximum 40° C., and the thermal death-point about 56° C. In gelatin stab cultures a round whitish surface elevation develops, from the center of which, a long, narrow, pin-like projection extends downward into the medium ("nail-growth"). The gelatin near the growth may darken, gas sometimes forms, but liquefaction does not occur. On agar and serum the whitish or faintly yellowish-white, smooth, often glistening growth follows the course of the needle stroke. In saccharine media it produces acid with the liberation of gas, especially if chalk be added to the culture. Grimbert, Frankland, and others have shown

FIG. 71.—BACILLUS OF INFLUENZA. X 1000 diameters.

[1] See works referred to in foot-note on page 81. Philippi, "Münch. med. Woch.," 1902, No. 45, p. 1884. Baumgärten, "Wien. klin. Woch.," Sept. 8, 1904, p. 966. Bernstein, "Amer. Jour. of the Med. Sci.," December, 1903. Stuehlern, "Centralbl. f. Bakt.," xxxvi, No. 4. This organism belongs to a group for which Fricke proposed the name Bacillus mucosus capsulatus.

that all the members of this group (the Bacillus mucosus capsulatus group) do not give rise to the same fermentative changes.

Demonstration.—The organism stains with the usual anilin dyes but not by Gram's method; to the latter statement, however, there are occasional exceptions. For staining the capsule in properly fixed spreads or in section Friedländer recommends the following: (1) Stain in the following solution for twenty-four hours:

Saturated alcoholic solution of gentian-violet, ...	50	parts.
Distilled water, ...	100	"
Acetic acid, ...	10	"

(2) wash one or two minutes in one per cent. aqueous solution of acetic acid; (3) dehydrate in alcohol; (4) clear in cedar oil; (5) mount in xylol balsam.

Pathogenesis.—Although mice, guinea-pigs, and rabbits are refractory to small doses, they can be infected. The organism is sometimes found in the nasal mucosa of normal individuals. It occurs in from five to eight per cent. of the cases of croupous pneumonias and in about fifteen per cent. of the bronchopneumonias. The studies of Baumgärten, Stuehlern, and others indicate that it may be an independent exciter of croupous pneumonia, although usually it is associated with the pneumococcus. Occasionally the bacillus is present in endocarditis, pericarditis, and otitis media; it has been obtained from the blood during life. Cionnini[1] has collected 24 cases of angina resembling diphtheria but due to the bacillus of Friedländer. Étienne has shown that it is present in many infections; the organism has been obatined in pure culture from pus. It has been encountered in pyelonephritis, cystitis, and infections of the tunica vaginalis testis, epididymis, and testicle. Occasionally it produces a true septicemia, as in the case reported by Jenssen.[2]

Pestis,[3] **Plague, Bubonic Plague, Oriental Plague, or Pestilentia** is a specific infectious disease, endemic in certain parts of Asia and Africa, in which regions and elsewhere the affection sometimes assumes epidemic proportions. The **Bacillus pestis** is a short rod with rounded ends, sometimes designated a coccobacillus; it measures 0.3 μ to 0.7 μ in width and 1 μ to 4 μ in length. In cultures chains of coccoid bacilli develop and the length of detached organisms varies more than in the

[1] "Rif. Med.," June 17, 1903.

[2] "Münch. med. Woch.," July 21, 1903, p. 1250

[3] See works referred to in foot-note, p. 81 Flexner, "Univ. of Penna. Med. Bulletin," Aug., 1901. Goss, "Arch. des Sci. Biol. de Saint Petersburg," 1904, No. 5, p. 429. Zinno, "Arch. de med. exper. et Anat. Path.," Jan., 1904, p. 1. Handi, "Zeit. f. Hyg. u. Infectkrank.," 1904, Bd. 48, Heft 3. Bielonovsky, "Arch. des Sci. Biol. de Saint Petersburg," 1904, vol. x. Kolle, "Zeit. f. Hyg. u. Infectkrank.," Bd. xlviii, p. 368. Thiroux, "Annales de l'Inst. Pasteur," Jan. 25, 1905, p. 62. White, "Med. Record," Jan. 28, 1905. Calvert, "Jour. Amer. Med. Assoc.," Jan. 16, 1904. Rosenau, Bulletin No. 4 of the Hygienic Laboratory, 1901. Harris and Arnold, "Phila. Med. Jour.," April 7, 1900. Herzog and Hare, "Jour. Amer. Med. Assoc.," Dec. 10, 1904, p. 1781. Hankin, "Jour. of Hygiene," Jan., 1905, p. 48. Zlatogoroff, "Centralbl. f. Bakt.," Bd. xxxvi, xxxvii, 1904. Durck, "Ziegler's Beitr.," Supplementary Heft, 1904, exhaustive study of pathological anatomy with full bibliography. Herzog, Bulletin No. 23, October, 1904, Biological Laboratories, Department of the Interior, Bureau of Government Laboratories. Herzog, "Amer. Jour. of Med. Sci.," March, 1905, p. 504, "Suctorial and Other Insects as Plague-carriers."

tissues. Polar staining is more marked in bacilli contained in the tissues than in those derived from cultures. In agar containing two to three per cent. sodium chlorid, yeast-like forms may be present; this reaction is of value in identifying the organism. In gelatin the bacillus at 22° C. forms small, round, granular, yellowish, refractile and semi-transparent colonies without liquefaction. The colonies on agar are whitish and slightly transparent with irregular borders; the growth clouds bouillon slowly, and after some days deposits a flocculent sediment. A few drops of cocoanut oil or melted butter on the surface of the last-named medium causes the production of growths extending downward as conical, long, shaggy, thread-like projections. These "stalactite" cultures develop only when the medium is perfectly still, the slightest agitation detaching the pendulous masses; stalactite formation is of great diagnostic value. The organism grows most luxuriantly in alkaline media, but a faintly acid nutrient facilitates separation of the Bacillus pestis from the pneumococcus. The minimum temperature is about 20° C. or slightly below, the optimum 37° C., above which point the organism does not grow well; Abel's experiments show that it is killed by boiling one minute, at 90° C. in five minutes, at 70° C. in ten minutes, and often dies after one hour's exposure to 55° C. The bacillus is slightly motile, flagellated, produces indol, and is aerobic, although feeble growths may be obtained when air is excluded. The **toxins** produced by the Bacillus pestis are largely, although not exclusively, intracellular. Experimental studies and the abundance with which the bacillus is found in the tissues indicate that the organism is not highly toxic, certainly not in the sense that diphtheria, tetanus, and allied bacteria are.

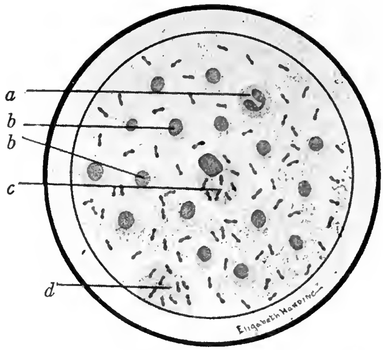


FIG. 72.—HIGHLY MAGNIFIED PORTION OF A NECROTIC LYMPH-NODE SHOWING PEST BACILLI.

Specimen fixed in solution of Foa, embedded in paraffin and stained in carbol-toluidin blue forty-eight hours, and differentiated by glycerin-ether.—(*Harris.*) Zeiss "*b*" eye-piece and $\frac{1}{12}$ inch homogeneous oil-immersion objective. *a.* Polymorphonuclear leukocyte. *b, b.* Lymphoid cells. *c.* Phagocyte containing pest bacilli. *d.* Degenerating phagocyte containing bacilli. The nucleus of this cell has disappeared.

Demonstration.—In cases of suspected plague an enlarged gland, through a previously asepticized field, should be punctured by a hypodermic needle. From the fluid obtained in this way cover-glass spreads and cultures should be made and rats and guinea-pigs inoculated. Blood cultures are often of great value and should be obtained whenever possible. Open or discharging buboes frequently contain so many concurrent organisms that there may be difficulty in isolating the plague bacillus. In the cadaver inoculations and spreads from the blood and viscera, and particularly the spleen, will yield data requisite for diagnosis. Inoculated animals usually manifest more or less local infiltration and necrosis, the adjacent lymph-nodes enlarge, bacteremia is commonly rapidly developed, and death frequently occurs in from two to five days. The bacilli are abundantly present in the blood and organs, and from both they may be demonstrated in films. The Bacillus pestis

stains with the usual anilin dyes but not by Gram's method. Carbol-fuchsin diluted with nine parts of water may be used, but the best results are obtained with carbol-thionin or carbol-toluidin blue; prolonged differentiation can not be employed.

Pathogenesis.—In man infection occurs by (1) the skin, (2) inhaled bacilli, or (3) through the alimentary canal. It is commonly stated that plague may be transmitted from animal to animal or from animal to man, through the intervention of insects, particularly fleas. In a number of epidemics data supporting this belief have been obtained. Nuttall has studied the question experimentally and his observations do not support the theory. Rats are particularly susceptible to plague and are commonly infested with fleas. It has been shown that viable plague bacilli may be present in the bodies of these insects, and that certainly they may convey the disease even though there be some doubt as to their inoculating the bacillus into man. Three forms of the pest are usually described: (1) the bubonic, which may be mild or malignant, (2) pest pneumonia, primary or secondary, and (3) the septicemic form. Cases of latent and ambulatory plague undoubtedly occur, and possibly constitute means by which the disease is disseminated. The studies of Herzog and Hare clearly show, however, that such cases are not common.

In bubonic plague any of the lymph-nodes may be primarily affected, the particular ones involved being determined by the point of inoculation. Among people who habitually go bare-footed the inguinal glands commonly first manifest the disease. In laborers, with infection through the upper extremities the axillary glands are involved; in other instances the cervical lymph-nodes show the first manifestations of the disease. Systematic writers commonly divide the buboes into two groups, primary and secondary. The **primary bubo** developing immediately as the result of infection, and contiguous to the point through which the bacillus entered, is called a **primary bubo of the first order**; the lymph-nodes that enlarge immediately adjacent to this lesion and are infected from it, constitute **primary buboes of the second order.** Buboes resulting from systemic distribution of the bacilli are called **secondary buboes.** The rapidity with which the primary buboes form, and the intensity of the alterations taking place in the lymph-nodes, vary from slight indolent chronic swellings to rapid enlargements with progressive softening due to necrosis of the gland substance and accumulated cells. In frank cases periglandular infection rapidly develops and the enlarged nodes soon become embedded in edematous, cell-infiltrated, or partly necrotic connective tissue. Histologically the lymph-nodes contain large numbers of the bacilli, and in the earlier stages, before necrosis has destroyed the affected tissue, fibrin and numerous leukocytes are also present. Usually these cells are mostly of the mononuclear type, many of them large and actively phagocytic, and containing numerous pest bacilli. Harris has shown that mast cells are frequently found. Polymorphonuclear leukocytes are not abundant, and in the absence of pyogenic infection the process is one of necrosis and softening rather than an acute suppuration. The blood-vessels of the nodes are usually thrombosed, the endothelium swollen and desquamating, and the walls often destroyed.

Pneumonic plague (plague pneumonia) may follow the bubonic

type, or result from inhalation of the organism. The lesion produced is of the lobular type, although a lobe or more may be solidified. In addition to the hepatized areas the organ is the seat of numerous hemorrhages, edema, mucopurulent bronchitis, and sometimes a fibrinous exudate covers the overlying pleura; the bacilli are abundantly present in the sputum during life and in the lung, bronchi, and peribronchial glands postmortem.

The bubonic and pneumonic forms of plague, particularly the latter, commonly terminate in the **septicemic form.** Cases of plague bacillemia occasionally occur when no primary point of infection can be identified, and the bacteria may be present in the circulation of patients who afterward recover.

When death has resulted from the disease, early and marked rigor mortis and postmortem lividity are usually present. The temperature may rise after death.

Buboes which may be suppurating are sometimes found and conjunctival infection may be evident. The muscles are frequently dark; the serous cavities are usually dry and numerous petechiæ or ecchymotic areas may fleck the subserosa. The blood is dark, often without clots. The spleen is enlarged, soft, dark in color, and on microscopic examination the sinuses are dilated, the leukocytes increased in number, areas of necrosis are present, phagocytes often abundant, and the characteristic bacilli invariably demonstrable, usually in large numbers. The kidneys are frequently slightly enlarged, soft, drip blood on section, and contain areas of hemorrhage. The epithelium is usually granular and bacilli can be demonstrated in the vessels and tufts. Herzog describes and figures the presence of hyaline thrombi in the renal glomeruli. The liver is frequently slightly enlarged and may contain areas of necrosis. Wilms observed marked swelling, necrosis, and hemorrhage in the solitary and agminated follicles of the intestine, hemorrhages in the mucosa, and enlarged mesenteric glands often containing necrotic and hemorrhagic foci. The brain and spinal cord are sometimes congested and in rare instances fibrinous meningitis and meningoencephalitis have been observed. Congestion, proliferative processes, and necrotic lesions occur in the bone-marrow.

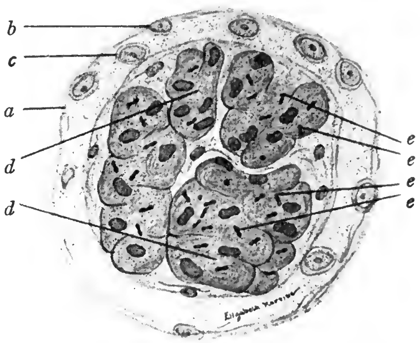


FIG. 73.—SECTION OF KIDNEY SHOWING MALPIGHIAN BODY CONTAINING PEST BACILLI.

Section fixed in Foa solution, embedded in paraffin and stained in carbol-toluidin blue and differentiated by glycerin-ether. Zeiss "b" eye-piece and $\frac{1}{12}$ inch homogeneous oil-immersion objective.

a. Capsule of Bowman. *b.* Epithelial cells lining capsule, some of which (*c*) have desquamated. *d, d.* Capillaries in glomerule, in the interior of which (*e, e, e, e*) are many pest-bacilli.

An **antitoxin** may be prepared by the repeated intravenous injection of slowly increasing doses of pest bacilli until the animal acquires a marked immunity; the horse is usually used. In beginning the process of immunization it may be well to employ killed cultures, followed later by living bacilli. The value of plague anti-sera has not been uniformly attested.

Haffkine's **protective vaccination** is undoubtedly of very great value The vaccine used is prepared from cultures of the bacillus in bouillon, the surface pellicle being allowed to develop as often and fully as possible. The bacilli are killed by exposure to 65° C. for one hour and 0.5 per cent. carbolic acid added. From 5 c.c. to 10 c.c. of this fluid, depending upon its strength, is injected subcutaneously. The maximum protection is attained during the week following inoculation; the protective influence wanes but persists for months.

Chancroid, soft chancre, simple chancre, or non-infecting chancre is an ulcerative process usually affecting the genitals, propagated almost exclusively by venery, and due to the **Bacillus ulceris mollis**[1] (Ducrey). The bacillus is 1.5 μ in length, 0.5 μ in thickness, with rounded ends which usually stain more deeply than the central part of the rod. In cultures long, dot-like chains are produced. Pure cultures have been obtained by a number of observers; the germ does not grow on the usual laboratory media, but can be cultivated on rabbit's blood-serum. Davis secured cultures on alkaline agar containing one-third rabbit's blood, but regards freshly drawn human blood as the best medium. After twenty-four hours at 37° C. delicate flocculi appear in fluid media or the water of condensation when blood agar is used. By flowing the fluid over the surface round, grayish colonies appear in forty-eight hours. Evidence of spore formation has not been observed.

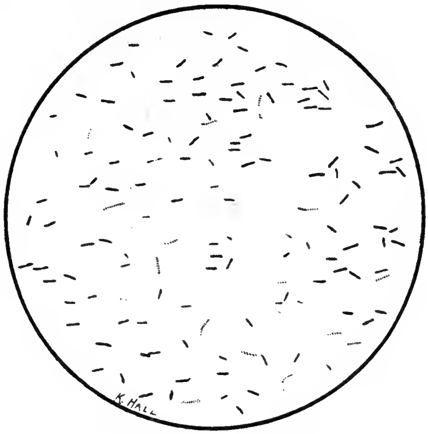


FIG. 74.—BACILLUS OF SOFT CHANCRE

Demonstration.—The organism stains readily, but is easily decolorized. Nicolle recommends carbol-toluidin blue, and Unna, polychrome methylene-blue. For staining bacilli from cultures, Davis advises the use of carbol-fuchsin followed by brief differentiation in alcohol, thereby bringing out the polar bodies. The organism is Gram-negative, and quite difficult to stain in sections.

Pathogenesis.—Nicolle was the first to inoculate the monkey successfully; the ordinary laboratory animals are immune. The lesion produced in man is rarely extragenital. Ullman has been able to collect 64 extragenital chancroids. It develops as a red point advancing to a papule, and later pustule, which ruptures, exposing a deep, crater-like ulcer the edges of which are often undermined and the discharge abundant. The ulcers sometimes take on phagedenic action and produce wide-spread destruction. The lymph-nodes, anatomically nearest the lesion, enlarge and may suppurate (chancroidal bubo). In some cases there is an intense, often polymicrobic, mixed infection with other organisms, usually of the pyogenic group.

[1] See works referred to in foot-note, p. 81. The most important references to this organism can be obtained from paper by Davis, "Jour. Med. Research," June, 1903, p. 401.

Conjunctivitis may be produced by a large number of organisms, including the streptococcus, pneumococcus, bacillus of Friedländer, the gonococcus, pyogenic staphylococci, xerosis bacillus, etc. Diphtheria sometimes attacks the conjunctiva. An acute, usually catarrhal but sometimes purulent inflammation of this tissue is produced by a small, immobile, Gram-negative organism resembling the influenza bacillus in morphology and cultural characters, and usually called the **Koch-Weeks bacillus,** after its discoverers. It is often seen in the interior of the polymorphonuclear leukocytes found in the conjunctival discharge. It is frequently united in pairs end to end and sometimes forms short chains. The bacillus of Weeks stains readily, but not intensely, with the ordinary anilin dyes. Cultures can not be obtained on ordinary laboratory media; the organism grows slowly on serum agar, blood agar, or serum; the best medium for its cultivation is agar containing one-third ascitic fluid.

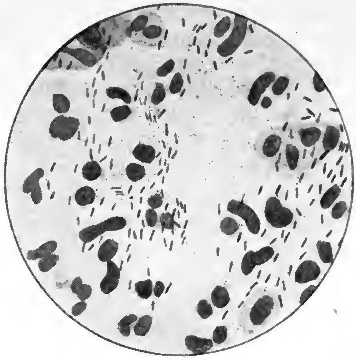


FIG. 75.—THE KOCH-WEEKS BACILLUS.—(*Hansell and Sweet.*) ×950.

The so-called **diplobacillary conjunctivitis** is due to the **Bacillus lacunatus**[1] (Morax-Axenfeld). This organism is 2 μ in length, 0.7 μ to 1 μ in thickness, arranged in pairs placed end to end, and sometimes in short chains of four to six elements. It does not grow below 30° C. nor above 40° C.; the optimum temperature is 37° C., and the thermal death-point 56° C. It is an optional anaerobe, non-motile, and does not produce spores. In streak cultures on the surface of serum a moist, shining growth develops along the line of inoculation. The solidified serum is gradually liquefied, forming a furrow, which at first extends in depth only, but later widens. Smear cultures develop as individual colonies, which pit the serum. After cultivation through a series of serum tubes the organism may, in some instances, be grown upon agar, where it then forms "translucent, discrete colonies, like dewdrops." In bouillon containing one-third serum a turbidity quickly develops, which is not lessened by the occurrence of a grayish-white deposit on the sides and bottom of the tube. The organism requires frequent transplantation.

FIG. 76.—BACILLUS LACUNATUS.—(*Hansell and Sweet.*) ×950.

[1] See works referred to in foot-note, page 81. For careful study of this organism see paper by J. W. Eyre, M.S., M.D., in the "Journal of Path. and Bact.," vol. vi, No. 1, May, 1899.

Demonstration.—The Bacillus lacunatus stains slowly but clearly with the usual anilin dyes; the best results are obtained with an aqueous solution of *Bleu de Roux.* The reaction to Gram's stain is peculiar, partial decolorization taking place; the staining is never characteristically that generally obtained by Gram's method. This peculiarity is to be utilized in identifying the organism.

Pathogenesis.—The bacillus is not pathogenic for animals. In man it is found in cases of subacute and chronic conjunctivitis and may be present in large numbers. The disease has been produced experimentally by inoculating the human conjunctiva.

The **Bacillus pyocyaneus**[1] (Gessard, 1882) is a short delicate rod 1 μ to 1.5 μ long, 0.5 μ wide, motile, aerobic, and growing readily at temperatures between 20° C. and 37° C. Under various influences, particularly the addition of an antiseptic to the medium, long chains, irregular rods, and even spirals may be produced; gelatin is liquefied, and in this medium as well as bouillon, agar, and milk a greenish tinge is produced; on solid media the surface presents a peculiar metallic luster. In addition to the greenish pigment (pyocyanin) the organism produces pyoxanthose, pyofluorescin, a mucinoid substance, and both intracellular and extracellular toxins.

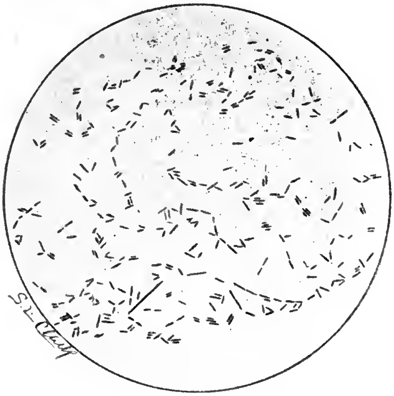


FIG 77.—BACILLUS PYOCYANEUS.

Demonstration.—The Bacillus pyocyaneus stains by the usual anilin dyes and is Gram-negative. By plate methods it is easily isolated.

Pathogenesis.—The organism is frequently found in green pus and in intestinal discharges, particularly in the diarrheas of infancy. Numerous cases of pyocyaneus septicemia have been reported. It has been found in angina, peritonitis, pericarditis, pleurisy, various skin eruptions, otitis media, and cystitis. Jadkewitsch has described certain nervous manifestations attributed to this organism. It may produce catarrhal conditions of the mucosa which occasionally go on to ulceration; rarely it induces a hemorrhagic enteritis; parenchymatous degeneration of the liver and kidney is sometimes present; the spleen enlarges and may contain areas of necrosis. Among the products of this organism is a definite hemolytic substance (pyocyanolysin); one of the remarkable peculiarities of this body is its extraordinary resistance to heat; the hemolytic power is not destroyed by exposure to 120° C. in the autoclave.

Gaseous emphysema and other lesions may be produced in man and

[1] See works referred to in foot-note, p. 81. MacIntyre, "Jour. Amer. Med. Assoc.," April 23, 1904, p. 1075, "Intracellular Toxins." Barth and Michaux, "La Presse Med.," May 30, 1903, p. 405, "Pyocyaneus Cystitis." Eastman and Keene, "Annals of Surgery," Nov., 1904, "Pyocyaneus Septicemia." Jordan, "Trans. Chicago Path. Soc.," Dec. 8, 1902, "On the Nature of Pyocyanolysin."

lower animals as the result of infection by the **Bacillus aërogenes capsulatus.**[1] The organism measures 3 μ to 6 μ in length and 1 μ to 1.5 μ in thickness. The bacillus is a strict anaerobe. In cultures long filaments and chains are often formed. It usually produces spores, but sometimes does not. It is also fickle in its liquefying action on gelatin and in the production of capsules; usually both are positive. Gas formation is generally present in cultures, it softens without frankly liquefying gelatin, and coagulates milk with the production of gas and acid. There is a slight tendency to liquefy solidified serum. The bacillus ferments lactose, saccharose, and mannite. It grows at ordinary room-temperature, but best at 37° C.; spore-free cultures are killed by 58° C. in ten minutes; the spores require ten minutes' boiling.

Demonstration.—For obtaining pure cultures Welch recommends injecting 0.5 c.c. to 1 c.c. of a twenty-four-hour old milk culture—or suspension of a surface growth on agar—into the ear vein of a rabbit, which in two or three minutes is killed and placed in the incubator. After seven or eight hours the body will be found distended with gas, bubbles of which may be seen in the blood, heart cavities and viscera. The gas is inflammable. The bacillus stains with the usual anilin dyes; in tissues it is Gram-positive; the stain reaction of spreads from cultures is not constant.

Pathogenesis.—The virulence of different strains of the organism is not uniform; some cultures possess but slight pathogenic power. The guinea-pig is the most susceptible of the laboratory animals. In man the organism has been found associated with emphysematous gangrene, gaseous abscesses, genito-urinary and gastro-intestinal affections, inflammation of the pleuræ and meninges, puerperal and other infections of the uterus, and, postmortem, is a frequent cause of cavity formation in the viscera (foam-organs, *emphysema cadaverosum*). It has been obtained in pure culture from the blood during life. Leroy found it in a wound six days before death of the patient. In the infections with which it occurs it is frequently associated with other pathogenic bacteria.

Emphysematous gangrene, gaseous abscess, and allied conditions in which gas is found in the tissues, may be produced by other organisms than those just mentioned. Jacobelli described an organism, which he calls the Bacillus septicus aerobicus, isolated from two cases of gaseous gangrene. It is not gas-producing in saccharine media. Howard reports an instance of acute fibrinopurulent meningitis with gas cysts in the brain due to the Bacillus mucosus capsulatus. Regnault[2] maintains that there is no special organism in the lesions associated with gas-productions and has collated numerous reported cases of gaseous abscess and gangrene, some of which were due to the colon bacillus, Bacillus perfringens, and other organisms. Legros has reached similar conclusions. The bacteria producing gas in the tissues may also give

[1] See works referred to in foot-note, p. 81. Cole, "Bulletin of the Johns Hopkins Hospital," Oct., 1902. Fränkel, "Virchow's Arch.," 1904, Bd. 177, p. 175; Werner, "Arch. f. Hyg.," 1904, Bd. 1, Heft 3. Leroy, "Jour. Amer. Med. Assoc.," Oct. 24, 1903, p. 1009. Dudgeon and Sargent, "Path. Soc. of London," Nov. 15, 1904. The organism was first described by Welch and Nuttall, "Johns Hopkins Hospital Bulletin," 1892, vol. 3. In the Shattuck Lecture ("Bull. Johns Hopkins Hosp.," Sept., 1900) Welch gives extended data concerning the organism and the lesions produced by it.

[2] "Revue de Chir.," July, 1903, p. 77.

rise to degenerative and necrotic changes in the muscles associated with serous, serofibrinous, or serocellular exudates.

Malignant edema[1] is an acute infiltrating inflammatory process characterized by more or less swelling and rapid tissue necrosis terminating in gangrene, and due to an anaerobic, spore-bearing, motile organism called by Pasteur **Vibrion septique,** and by Koch the **Bacillus œdematis maligni.** The organism is 0.75 μ to 1 μ thick and 3 μ to 5 μ in length, sometimes forming filaments 15 μ to 40 μ long. The optimum temperature is 37 ° C.; the organism may be obtained in culture at 15° C.; non-spore-bearing rods are killed at 60° C.; the spore withstands boiling five to ten minutes. In the depth of agar cultures it appears as small c ouds which Gould has well described as fuzzy masses; gas is produced. Similar colonies are developed in gelatin with liquefaction of the medium and evolution of gas; milk is coagulated.

Demonstration.—The bacillus of malignant edema stains with the usual anilin dyes and is Gram-negative; in peritoneal exudate it may be Gram-positive. Subcutaneous inoculation in the guinea-pig gives rise to hemorrhagic edema, exudation into the serous cavities, moderate gas formation in the connective tissues, and death; successive passages through these animals increases the virulence of the bacillus.

Pathogenesis.—The germ is pathogenic for man, guinea-pig, white rat, mouse, cat, sheep, goat, and horse. The chicken, pigeon, and ass are less susceptible; in dogs often no lesion is produced. Cattle are refractory to experimental inoculation, but occasionally contract the disease. The bacillus is usua ly associated with other organisms although there are a number of cases in which it has been found alone. Pasteur showed that the filtered exudate contains a poison fatal to guinea-pigs, and several experimenters have obtained toxic substances from cultures. According to Kerry, the bacillus decomposes albumen with the production of the usual putrefactive substances, including fatty acids, leucin, etc. Animals may be immunized against the toxin and in this way rendered insusceptible to infection by virulent bacilli.

The **Bacillus coli communis**[2] is the most common inhabitant of the intestine of man and many lower animals. The organism is 1.6 μ to 3.2 μ in length, and 0.4 μ to 0.8 μ in breadth. Oval, coccoid, and diplococcoid forms have been described; filaments are sometimes formed. The germ is commonly motile and flagellated, non-spore-bearing and usually gas-producing; it is aerobic, but can grow without oxygen. On gelatin plates it forms small, flat, grayish colonies with irregular outline

[1] See works referred to in foot-note on p. 81. A recent detailed report of a case and references to other cases in literature, see Gould, "Annals of Surgery," October, 1903.

[2] See works referred to in foot-note, p. 81. The literature bearing on this subject is too exhaustive to be quoted, but may be traced from the following references: Savage, "Jour. of Path. and Bact.," Nov., 1904, p. 90. Moore and Revis, "Jour. of Path. and Bact.," Nov., 1904. Gérard, "Soc. de Biol.," March 4, 1905. Vaughan, "Jour. Amer. Med. Assoc.," Sept. 3, 1904, p. 643. Moore, "Medicine," March, 1903, p. 189. Savage, "Jour. Path. and Bact.," March, 1904, p. 347. Ford, "Classification and Distribution of Intestinal Bacteria in Man," Studies from the Royal Victoria Hospital, Montreal, vol. i, No. 5 (Pathology, II); an exhaustive review of the intestinal bacteria. Moorhead, "The Practitioner," June, 1905, discusses septicemia due to the organism, with review of literature. Trautner, "Nord. Med. Arkiv.," 1904, Afd. ii, Heft 2, No. 7.

and does not liquefy the medium. Stab cultures in gelatin give rise to a faint grayish film on the surface and a grayish-white streak along the track of the needle, with the evolution of gas. On potato the growth is moist, relatively rapid, and in older cultures assumes a brownish tinge. Milk is usually coagulated, although some cultures require weeks to induce the change; acid is produced. Some strains of the organism vary from the foregoing rather typical cultures; gas production may be inconspicuous or absent, motility scarcely perceptible and milk coagulation long delayed. The most prominent distinguishing differences between this and closely allied pathogenic organisms are given in table on page 140.

Demonstration.—The colon bacillus is readily cultivated and may be grown upon all the laboratory media. It may be stained with the usual anilin dyes, but requires prolonged exposure to the staining fluid, is easily decolorized, and does not bear active differentiation; it is Gram-negative.

Pathogenesis.—Lesage and Macaigne called attention to the fact that the colon bacillus found in diarrhea and intestinal inflammations is more virulent than when obtained from normal stools; Ferranini demonstrated that the organism was more toxic for emaciated than for well-nourished animals. These observations, which have been corroborated by others, establish two facts: (1) The colon bacillus varies in its toxicity and pathogenesis, and (2) the resistance of the individual to colon infections is profoundly influenced by the state of the body nutrition. Martin, Carega, Vaughan, and others have shown that the colon bacillus (some strains at least) is capable of elaborating a poison the toxicity of which is not constant. Vaughan's studies give us considerable information as to the character of the intracellular toxin produced by the germ. In the tissues under different conditions changes produced by colon infection indicate that the poison is not always the same, or at least in different strengths it may cause dissimiliar changes. The possibilities of chronic subinfection by the colon bacillus have been mentioned on page 89. It is probable, as indicated by the studies of Ford, that the colon bacillus frequently enters the tissues, but in such small numbers that some special condition must favor its colonization and the production of definite changes. The germ has been found in a great many pathologic processes, sometimes alone and often associated with other bacteria. This fact renders it difficult to determine exactly what alterations are due to the colon bacillus alone and which are induced by the bacteria with which it occurs. Some strains of the bacillus are definitely pyogenic and may, without the presence of any other microbe, give rise to definite suppurative processes. It has been isolated in pure culture from abscesses, osteomyelitis, peritonitis, pleurisy, pericarditis, inflammations of the genito-urinary and reproductive organs, meningitis, arthritis, gall-bladder and biliary passages, hepatic inflammations both acute and chronic, otitis media, conjunctivitis, pancreatitis, mastitis, and may be the only demonstrable organism in infected wounds. In many cases of appendicitis it is the only microbe present, and this disease, in the absence of the colon bacillus, can not be said to be common. In the complications and sequelæ of typhoid fever the colon bacillus may be found alone or with the Bacillus typhosus. When any local lesion affecting the circulation of any part of the intestine (constriction, strangulation, thrombosis, embolism)

lessens the resistance of the intestinal wall, the colon bacillus, alone or with other bacteria, infiltrates the affected tissues and plays a most important part in the necrotic and inflammatory processes that follow. It is, therefore, a frequent organism in inflamed hernial sacs and in peritonitis; it has been abundantly proved that the colon bacillus may reach the peritoneum without any demonstrable solution in the continuity of the intestinal wall. Lesions in viscera adjacent to the intestine are not infrequently associated with the presence of colon bacilli in such a way as to indicate that the organism must have reached the affected structures by way of the circulation. This view is especially supported by the constancy with which the colon bacillus is found in the suppurative pelvic lesions of the female, in splenic abscesses and infarcts, and in the tissues of the spleen after its circulation has been interfered with by occlusion of the artery, or vein, or by traction upon, or torsion of, the splenic pedicle. The colon bacillus is often the only organism present in gallstones, and a number of observers have demonstrated that colon infection of the gallbladder and biliary passages may be followed by the formations of concretions. Gérard has shown that it decomposes the biliary salts and causes precipitation of cholesterin. Moorhead has fully established that the organism may produce a definite septicemia, including an associated endocarditis. The colon bacillus has been obtained in pure culture from the blood, and is not infrequently the only microbe found in the tissues postmortem.

Closely related to the colon bacillus are the Bacillus enteritidis of Gärtner, now known to be a member of a group rather than a distinct organism, a number of bacilli isolated from the intestine by Booker and by Sternberg and others, and the paracolon bacillus of Gilbert and its allies.[1] The scope of this book does not permit a full consideration of these organisms nor their relation to various pathologic processes with which they occur. At present we are sadly in need of some authoritative study that will definitely establish their position among the bacteria, particularly their relation to the colon, typhoid, and dysentery bacilli, and to the various pathologic processes in which they have been found.

The morbid anatomy of paracolon infection will be considered with the lesions of typhoid fever in the chapter on Diseases of the Alimentary Canal in Part III of this work. The cultural resemblance of the paratyphoid bacilli to the colon organism is given in the table on p. 140. All members of this group are capable of inducing inflammatory and necrotic processes, and in the blood give rise to agglutinins (which do not appear to be specific); in addition, they are toxicogenic.

Typhoid fever[2] is an acute infectious disease, usually water-borne,

[1] The literature bearing on these organisms will be found in the excellent studies of Cushing, "Johns Hopkins Hospital Bulletin," July and August, 1904, p. 156, and Fox, "Univ. of Penna. Med. Bulletin," April, 1905.

[2] A very full bibliography of the subject will be found in Nothnagel's "System of Medicine," American edition, volume on "Typhoid and Typhus Fevers," edited by Osler, 1902. Studies in Typhoid Fever, "Bulletin of the Johns Hopkins Hosp.," vols. iv, v, and viii. The following more recent papers may be consulted with regard to the disease and its organism: Fränkel, "Münch. med. Woch.," Jan. 12, 1904, p. 64. Rolly, "Münch. med. Woch.," June 14, 1904. Rodet, Lagriffoul and Wahby, "Arch. de méd. exp. et d'Anat. Path.," July, 1904. Rüdiger, "Trans. Chicago Path. Soc.," Feb. 8, 1904. Memmi, "Rif. Med.," 1904, No. 32. Front and also Jordal, Russell and Zeitt. "Jour. of Infectious Diseases," Nov. 5, 1904. Duchacek, "Centralbl. f. Bakt.," Oct. 17, 1904,

and generally believed to be due to the **Bacillus typhosus.** The morbid anatomy and complications of the affection will be discussed in Part III of this book, in the chapter on Diseases of the Alimentary Canal. Although infection usually occurs from drinking water containing the specific organism, epidemics have been traced to infected milk and to cress and salads contaminated by contact with water containing the germ. The microbe is readily conveyed by flies and possibly other insects, and may in this way be transported from place to place.

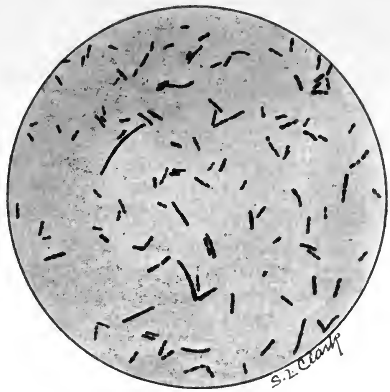


FIG. 78.—BACILLUS TYPHOSUS. Pure culture containing a few irregular forms.

The Bacillus typhosus is rod-shaped, 1.5 μ to 3.5 μ in length and 0.5 μ thick; longer filaments are sometimes formed. Although growths are readily obtained at room temperature and even at 15° C., the germ develops best at 37° C. and is killed by five minutes' exposure to 60° C. The typical organism possesses flagella, is actively motile, can be grown anaerobically, but develops best in an atmosphere containing oxygen; it grows readily on most of the laboratory media, the surface colonies resembling some strains of the colon bacillus; it does not liquefy gelatin nor produce gas. The colonies are more transparent than typical colon growths and the development is somewhat slower. Its growth on potato, long supposed of great diagnostic worth, has recently been shown to be so inconstant that it is no longer given much weight in identifying the organism. Usually on fresh potato, normally acid in reaction, no growth is visible for several days, and the rapidity of growth is never comparable to that of the typical colon germ. Other differentiating points of value are given in the table on page 140.

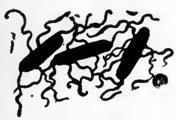


FIG. 79.—BACILLUS TYPHOSUS, SHOWING FLAGELLA.—(*Gould.*) $\times$ 1200 diameters.

Demonstration.—The typhoid bacillus stains with the usual anilin dyes and is Gram-negative. The microbe never stains intensely and does not withstand prolonged differentiation. Cultures are readily obtained and isolation may be accomplished by the usual plating methods.

Pathogenesis.—Most of the attempts to produce typhoid fever in animals have been entirely negative. It is not known that, under natural conditions, any of the lower animals are subject to the

p. 161, and Nov. 8, 1904, p. 326. Thayer, "Johns Hopkins Hospital Bulletin," Oct., 1904. Wright, "A Short Treatise on Antityphoid Inoculation," 1904; "Practitioner," March, 1904; "Brit. Med. Jour.," Nov. 12, 1904. Chantemesse, "La Presse Med.," Dec. 10, 1904. Natten-Larrier, "La Presse Med.," Dec. 7, 1904, p. 779. Voskressensky, "Prakt. Vratch," Nov. 20, 1904 (Typhoid contracted in the laboratory). Atlossoff, "Annales de l'Inst. Pasteur," Nov. 25, 1904, p. 701, on experimental production of typhoid in rabbits. For a few references to important papers on agglutination tests in typhoid, see chapter on Bacteriologic Technic

TABLE SHOWING RESEMBLANCES AND DISSIMILARITIES OF THE BACILLUS TYPHOSUS, BACILLUS COLI COMMUNIS, AND PARA-TYPHOID BACILLI, TYPES A AND B.

(COMPILED BY PROF. ROSENBERGER.)

	BACILLUS TYPHOSUS.	BACILLUS COLI COMMUNIS.	PARATYPHOID BACILLUS A.	PARATYPHOID BACILLUS B.
Motility,	Very active.	Usually motile.	Active.	Active.
Litmus milk,	May acidulate, never coagulates.	Acid reaction, generally coagulates.	Milk unchanged first four or five months.	First acid, later becomes alkaline.
Bouillon,	Cloudy, may form pellicle.	Cloudy, may form pellicle.	Cloudy, may form pellicle.	Cloudy, may form pellicle.
Potato,	Generally "invisible" growth.	Grayish-white to chocolate brown.	"Invisible" growth.	Yellowish brown.
Gelatin,	No gas, no liquefaction.	Gas, no liquefaction.	Gas may be formed, no liquefaction.	Gas may be formed, no liquefaction.
Malachite-green agar,	Colonies, round, glassy, surrounded by yellowish ring.	Rarely develops upon this medium.	Resembles typhoid bacillus.	Resembles typhoid bacillus, but yellowish ring is thicker and more marked.
Endo's medium,	Colonies transparent.	Colonies dark red with metallic lustre.	Colonies transparent.	Colonies transparent.
Neutral-red-lactose agar,	May turn yellow but no fluoresence. If yellow may again turn red.	Turns yellow with fluorescence.	Turns yellow with fluorescence.	Turns yellow with fluorescence.
Fermentation of carbohydrates and alcohols,	No fermentation.	Usually fermentation is produced with exception of melitose, amylum and inulin.	Ferments some of the carbohydrates.	Ferments some of the carbohydrates.
Agglutination with typhoid serum,	Almost constant.	Occasionally agglutinated.	Only occasionally agglutinated.	Only occasionally agglutinated.
Odor,	Not characteristic.	Usually fecal.	Not characteristic.	Not characteristic.
Indol,	Not produced.	Generally produced.	Not produced.	Not produced.
Drigalski-Conradi medium,	Colonies blue.	Colonies pink.	Colonies blue.	Colonies blue.
Hiss's[1] water-serum medium,	No coagulation.	Coagulation.	Not constant.	Not constant.
Toxin,	Intra- and extracellular.	Intracellular.	Intra- and extracellular.	Intra- and extracellular.
Pyogenesis,	Pyogenic.	Pyogenic.	Not pyogenic.	Not pyogenic.

[1] Hiss ("Jour. Med. Research," 1902, n. s., vol. iii) recommends for the differentiation of the colon and typhoid organisms a medium composed of horse serum one part, and sterile distilled water two to three parts. The mixture is rendered slightly alkaline to litmus, tinted with litmus tincture, and heated in an Arnold steam sterilizer, with cover off, until mixture becomes opalescent. The requisite percentage of any sugar desired is now added and the medium distributed in tubes which are sterilized in an Arnold steam sterilizer twenty to thirty minutes on three successive days. The colon bacillus turns the blue litmus pink, ferments the sugar, and coagulates the medium; the typhoid bacillus does not coagulate the medium nor ferment the sugar. Prof. Rosenberger has obtained the same results, using fluid from pleural effusion.

disease, a fact which militates against successful experimentation. Grünbaum believes that he has produced the disease in the monkey, and Atlossoff in rabbits. Inoculation experiments in the lower animals may give rise to bacteremia, and by passing the organism through rabbits or guinea-pigs its virulence may be materially exalted. With regard to the toxins produced by the germ we are not fully informed. The studies of Martin, Sanarelli, and Vaughan indicate that the most active poison generated by the microbe is an endotoxin. The necroses and endothelial proliferation that characterize typhoid infections are clearly of toxic action; the germ also produces a hemolysin. Animals may readily be immunized to the typhoid bacillus, and the serum of patients recovering from the disease possesses antityphoidal properties. In typhoid fever agglutinins for the bacillus are found in the blood and the Widal[1] test is of great value in diagnosis.

Antityphoid Vaccination.—Chantemesse and Widal in 1888 demonstrated the possibility of protecting mice against the typhoid bacillus, and in 1899 Chantemesse vaccinated his hospital internes by a method which has been worked out with greater detail by Wright. The same principle is applied as in vaccination against cholera, consisting of the hypodermic injection of suspended typhoid bacilli killed by exposure for five minutes at 60° C. A local reaction follows the injection, and by the end of a week or ten days the blood of the inoculated individual contains agglutinins and its bacteriolytic action toward the typhoid bacillus is materially increased. The dose of the vaccine depends upon the virulence of the organism; Wright uses a killed bouillon culture. The immunity produced is probably not great, nor of long duration. Whatever beneficial results may be obtained by the inoculation there is every reason to believe that they are increased by repeating the injection.

Dysentery is a form of colitis or enterocolitis, the morbid anatomy of which is considered in the chapter on Diseases of the Alimentary Canal. One form of the affection is caused by the Entamœba histolytica (p. 181) the other, endemic or epidemic dysentery, is believed to be of an infectious nature and due to the **Bacillus dysenteriæ,** recognized by Chantemesse and Widal (1888), but brought to its present position of prominence through the investigations of a number of observers, especially Shiga in Japan, Flexner in America, and Kruse[2] in Germany. There are clearly a number of strains of the organism, the cultural characters of each being fairly constant. Hiss recognized four groups, of which three produced indol and, on mannite, developed acid; two did not acidity maltose and saccharose; one produced acid on maltos, mannite,

[1] See Agglutination, chapter on Bacteriologic Technic.

[2] The literature of this subject has assumed colossal proportions. The most important studies are contained in, or may be traced from, the following: Shiga, "Zeit. f. Hyg.," 1902, Bd. xli, p. 355. Flexner, "Univ. of Penna. Med. Bulletin," Aug., 1901. Kruse, "Deut. med. Woch.," 1901, No. 23 u. 24; Broida, "Arch. de med. Exper. et Anat. Path.," Nov., 1903, p. 820. Eyre, "Edinburgh Med. Jour.," June, 1904, p. 489, a careful differential study of the dysentery bacilli. Holt, "Jour. Amer. Med. Assoc.," Dec. 24, 1904. Hiss, "Jour. of Med. Research," Dec., 1904, p. 1. Eisenberg, "Wien klin. Woch.," Oct. 27, 1904, p. 1142. Stein, Inaug. Diss., Bonn, No. 46, 1903. Jurgens, "Deut. med. Woch.," Nov. 12, 1903. Doerr, "Centralbl. f. Bakt.," 1905, Bd. xxxviii, p. 420. Also papers in "Studies from the Rockefeller Institute for Medical Research," vol. ii, 1904.

saccharose and dextrose; each produced acid in dextrose media. The bacillus is not motile, rarely if ever flagellate stains by the usual anilin dyes, but is Gram-negative. It is 1 μ to 3 μ long, 0.5 μ in diameter, and occasionally forms short threads; it possesses no capsule and is both aerobic and anaerobic. The optimum temperature is 37° C., but the organism grows between 18° G. and 42° C.; the thermal death-point is 60° C. Immunized animals and infected individuals produce antitoxins and agglutinins, the latter active in relatively high dilutions.

Pathogenesis.—Intestinal lesions may be produced in some of the lower animals by the administration of pure cultures by the mouth or subcutaneously. Part of a culture accidentally swallowed has been followed by dysentery in man. The organism evidently produces an active poison; the fact that killed cultures are much more toxic than the filtrate derived from living cultures indicates that this toxic substance is largely intracellular (endotoxin) or is composed of two constituents, the more active of which is intracellular.

The dysentery bacillus has been found in epidemics of the disease in the tropic, subtropic, and temperate climates, and in institutional dysenteries, such as are occasionally encountered in asylums and prisons. Numerous observers have isolated the organism from the intestinal contents of cases of enterocolitis in children, and an organism indistinguishable from the virulent form has been found in the feces of healthy children.

Gay and others have investigated the action of antitoxic sera which have been used in the treatment of dysentery. In some epidemics the serum treatment seems to have been of some value, although beneficial results have not invariably been observed. Anti-dysentery inoculations based on the same principles as anticholera vaccination have been tried.

Cholera[1] is a specific, infectious, communicable disease, practically always water-borne, and due to the **Spirillum choleræ asiaticæ** (Koch). The spirillum of Asiatic cholera consists of short comma-like elements 1.5 μ to 2.5 μ in length and 0.5 μ to 0.7 μ in thickness. In cultures U- and S-shaped forms and long spiral filaments occur. The organism is motile and flagellated (single flagellum, usually at one end only). It may be grown between 14° C. and 42° C.; the optimum temperature is 37° C., and thermal death-point 55° C. Spore formation does not occur. In old cultures involution forms, resembling yeast cells, some of which are suggestive of spores, are frequently present. The growth on gelatin is most characteristic. In gelatin plates the surface at first presents an appearance resembling that produced by sprinkling the medium with delicate glass splinters; this appearance is lost with beginning liquefaction. The gelatin plate should be kept at 22° C.; in about twenty-four hours liquefaction becomes evident, and usually progresses so that in a few days the entire plate is liquefied. Under the microscope the beginning colonies are granular with irregular borders, and white or yellowish-white in color. In stab cultures the growth begins at the surface and proceeds along the line of puncture. Liquefaction commences at the surface and

[1] See works referred to in foot-note, p. 81. Bibliography to the older literature will be found in Allbutt's "System of Medicine," vol. i. For methods of differentiating the organism, see Kraus, "Wien. klin. Woch.," Dec. 10, 1903, p. 1382. Tsuzuki and Myisaki, "Arch. f. Schiffs-und. Tropen Hyg.," July, 1903 and Hirschbruch and Schiver, "Centralbl. f. Bakt.," Sept. 12, 1903, p. 585.

accompanies the growth along the course of the needle-track. The area of liquefaction is funnel-shaped and a bubble-like expansion develops at a point corresponding to the junction of the tapering funnel stem and body. Milk is not coagulated. On agar and serum a thin whitish layer, later becoming brown, is produced; solidified serum is liquefied. Abundant growths can be obtained in Dunham's solution (1 per cent. peptone in water); cultures in this medium, twenty-four hours old, yield the indol reaction without the addition of nitrite. This is due to the spirillum reducing traces of nitrates present, rendering it necessary to add the sulphuric acid (1 to 2 drops) only. The reaction is sometimes called the nitro-indol or cholera-red reaction, and it is especially conclusive if it can be obtained by pure hydrochloric acid or oxalic acid.

A number of poisons have been isolated from the cultures and bodies of the germs, but the exact nature of these substances remains undetermined. Extracellular *toxins* have been separated from filtered cultures. The experiments of Metchnikoff and Pfeiffer indicate that the intracellular and extracellular poisons are not identical. Animals may readily be immunized against the organism, beginning with killed cultures followed by increasing doses of living spirilla. Such sera possess slight protective and therapeutic properties and may be used for agglutination or bacteriolytic studies necessary in identifying the organism. If the cholera spirillum be mixed with anticholera serum and injected into the peritoneum of a guinea-pig, bacteriolysis promptly occurs; the same result follows the injection of the organism into the peritoneum of an immunized animal. *Agglutinins* occur in the blood of immunized animals and in cholera patients.

FIG 80.—SPIRILLUM CHOLERA ASIATICÆ. PURE CULTURE.

Demonstration.—The spirillum of cholera stains by the usual anilin dyes and is Gram-negative. Carbol-fuchsin diluted with nine parts of water and used slightly warm is especially recommended. In suspected cases the organisms are present in such large numbers that during a cholera epidemic, the clinical diagnosis may be corroborated by microscopic examination of films prepared from typical stools. The Spirillum tyrogenum has different cultural characteristics. The spirillum of Finkler and Prior (cholera nostras) grows more rapidly, the colonies attaining a diameter of 2 or 3 cm. in forty-eight to fifty-two hours. The organism is less virulent than the cholera spirillum and is not agglutinated by the serum of cholera patients or cholera-immune animals. The cholera nostras spirillum gives the indol reaction much later; cultures are fetid and the stools from cases of cholera nostras much more offensive than those of true cholera.

Pathogenesis.—The influence of the cholera spirillum on animals has been referred to in the preceding paragraph. Animals under natural conditions appear immune against cholera and the typical disease

cannot be produced in them. By neutralizing the gastric juice and administering opium it has been possible to produce choleraic symptoms when virulent spirilla are given by the mouth. Similar results have occasionally followed intraduodenal injection of the organism. Laboratory workers have been infected by cultures.

Protective Inoculation.—Haffkine devised a method for securing a certain degree of immunity to cholera. Suspensions of cholera organisms, possessing low virulence, are injected subcutaneously, followed in four to six days by similar injections of highly virulent spirilla. The quantity of the injection, in each case, must depend upon the virulence of the organism, and can be determined by experiment only. This method of vaccination has been extensively used, particularly in India, and has been generally approved.

The cadaver, in cholera, often shows characteristic lesions. Rigor mortis comes on early and is often accompanied by postmortem contractions of the muscles. The skin, particularly of the palms of the hands, may be wrinkled and the features drawn. The tissues of the body appear abnormally dry, a result brought about by the abundant alvine discharges. Petechiæ and ecchymotic spots are sometimes present in the subserous tissues. The lungs, spleen, and liver show no constant change. The kidneys are swollen, congested, and may contain ecchymotic spots; the capsule is less firmly attached than normal and the renal epithelium shows more or less granular, fatty, and desquamative change. The most constant alterations are found in the intestine, the lesions becoming more intense from the jejunum to the ileocecal valve. The mucosa is swollen and frequently shows large denuded areas or smaller spots of desquamation; the solitary glands are often conspicuous and the patches of Peyer hyperemic and more or less tumefied. Sometimes the surface of the membrane is covered by a grayish diphtheroid film. The grayish, rice-water intestinal contents is loaded with desquamated epithelium, leukocytes, and varying numbers of red blood-cells. The cholera spirilla are particularly abundant. The lesions in the colon are of a similar kind, but less marked than those occurring in the ileum.

Tuberculosis.—The **Bacilli of tuberculosis**[1] are rather pleomorphic

[1] The literature on the tubercle bacillus is widely distributed, and the scope of this book does not permit full references. Should the Report of the Pennsylvania State Commission on Tuberculosis be printed, the paragraph on tubercle bacilli will contain references to nearly three hundred articles. Many of the older references will be found in the works referred to in foot-note on p. 81. Among the more recent publications that may be consulted are the following: "Tuberculosis and Acute General Miliary Tuberculosis," Nothnagel's "Encyclopedia of Practice of Medicine," American edition, 1904. Kober, "Amer. Jour. of Med. Sci.," Oct., 1903, p. 684, "Transmission of Bovine Tuberculosis to Man." Hayward, "N. Y. Med. Jour.," Oct. 1, 1904, p. 643, "Transmission of Tuberculosis by Insects." On the morphology of the organism consult Abbott and Gildersleeve, "Univ. of Penna. Med. Bull.," June, 1902. Most of the important literature bearing on the metabolic products of the bacillus is referred to by Bulloch and McLeod, "Jour. of Hygiene," vol. iv, No. 1, p. 1. On the tuberculins and their preparations consult Koch, "Deut. med. Woch.," 1897, No. 14, p. 209; Trudeau, Baldwin and Kinghorn, "Jour. of Med. Research," Aug., 1904, p. 169 "Tuberculin in Diagnosis," Tinker, "Johns Hopkins Hosp. Reports," 1903 vol. xi, p. 535. On thermal death-point see Theobald Smith, "Jour. of Exper Med.," 1899, vol. iv, p. 233; also Rullmann, "Berl. klin. Woch.," March 21 1904. On pathogenesis see Trudeau, "Trans. Assoc. of Amer. Phys.," 1903 vol. xviii, p. 97; Ravenel, "Jour. of Med. Research," Dec., 1903, p. 461; Theobald Smith, "Trans. Assoc. of Amer. Phys.," 1903, vol. xviii, p. 109.

organisms and it seems fairly established that they are closely related to the actinomyces; they are rod-shaped under certain conditions only, and might well be classed with the streptothrix group. It is possible to recognize three important divisions of the tubercle bacillus: (1) The tubercle bacillus of mammals. (2) The tubercle bacillus of birds. (3) The tubercle bacillus of poikilothermic animals.

The tubercle bacilli of mammals show certain morphologic and cultural differences depending upon the particular animals from which each organism is obtained. For this differentiation we are largely indebted to Theobald Smith. The following condensed description presents the important characters of the tubercle bacillus found in warm-blooded animals and particularly that pathogenic in man. It is an aerobic, non-motile, straight or slightly curved rod with rounded ends, 1.5 μ to 3.5 μ long and 0.25 μ to 0.5 μ thick; its optimum temperature is 37.5° C., the minimum 30° C., and the maximum rarely exceeds 40° C., although it can be made to grow at 45° C. The thermal death-point is about 68° C., although, under favorable conditions (for example, in sputum), the organism may resist 100° C. for fifteen minutes. The bacillus develops slowly upon suitable media, requiring from two to three weeks to make its appearance upon blood-serum —a medium especially adapted to its cultivation. It also grows upon glycerin agar and may be made to acquire the ability to grow upon glycerin-free media, although such growth is attained only after considerable difficulty. On the surface of solidified serum it appears as a cream-colored or whitish layer, usually dull, granular, and somewhat wrinkled; granularity and wrinkling become more marked as the culture ages, and finally the surface takes on a bread-crumb appearance. On glycerin-bouillon carefully floated fragments gradually extend, coating the surface with a finely granular, white or cream-colored layer with a dull surface eventually covering the medium and extending 1 mm. or 2 mm. upward on the side of the flask or tube. In older cultures the surface wrinkles, the pellicle saturates and sinks, after which some slight surface growth may redevelop; ordinarily, however, the second film is scanty and incomplete. The organism grows upon glycerin-agar, the cultures resembling those on serum. Cultures on vegetable media have been obtained.

FIG. 81.—BACILLUS TUBERCULOSIS. Branched and beaded forms from homogeneous culture of human origin.

Demonstration.—The tubercle bacillus resists the penetrating action of dyes, but once it has absorbed the stain is decolorized with difficulty; both these qualities are dependent upon the fat-like substance contained within the bacillary protoplasm. It can be stained with most of the basic anilin dyes and by Gram's method. It is more readily demonstrated in films than in sections; and in tissues supposed to contain the bacillus, better results are obtained from the expressed juices than in sections. Urine to be examined for tubercle bacilli should be subjected

to prolonged sedimentation by methods given in the chapter on Technic of Microscopic Examination of the Urine. Sputum may be taken as a type, and the method recommended for demonstrating the bacillus in expectoration can be applied to other pathologic fluids and exudates In the sputum search is made for yellowish, opaque, cheesy particles the finding of which is facilitated by spreading the liquid on glass or in the bottom of a large Petri dish. Selected material is spread in a thin, even layer on the surface of the slide or cover-glass, preferably the latter, and is allowed to dry in the air. The cover is then fixed by passing it through the flame, following the directions given in the chapter on Bacteriologic Technic. Flood the film with carbol-fuchsin and heat for three to five minutes, not allowing the stain to boil or become dry. Pour off the excess of stain, wash in water, and apply a few drops of Gabbet's acid methylene-blue, which should be evenly flooded over the film and allowed to act two or three minutes. Wash the film in water, and if all the red has not been discharged, reapply the Gabbet's solution; after the final washing in water, dry and mount in balsam. In successful preparations the tubercle bacilli appear as short red rods, while other bacteria, the ground-substance and nuclei of cellular elements, are stained blue. When time is no object, films or sections may be allowed to soak in the stain twelve to twenty-four hours at room-temperature, and it is probable that this method yields more satisfactory results than the more rapid one. The formula for carbol-fuchsin is given on page 49; Gabbet's acid methylene-blue counterstain is prepared by adding 2 gm. of methylene-blue to 100 c.c. of a twenty-five per cent. aqueous solution of sulphuric acid.

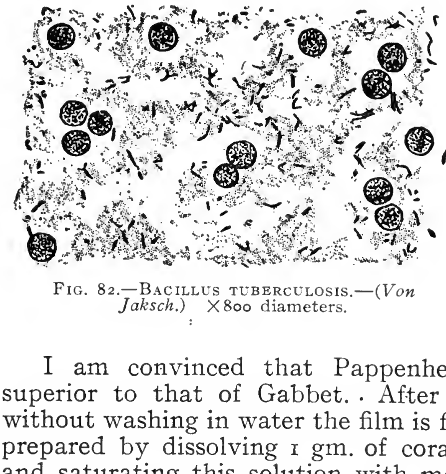


FIG. 82.—BACILLUS TUBERCULOSIS.—(*Von Jaksch.*) ×800 diameters.

I am convinced that Pappenheim's[1] method of decolorizing is superior to that of Gabbet. After staining with carbol-fuchsin and without washing in water the film is flooded with a decolorizing solution prepared by dissolving 1 gm. of coralin[2] in 100 c.c. of absolute alcohol and saturating this solution with methylene-blue, after which add 20 gm. of glycerin. The decolorizing solution is poured off and fresh applied, this step being repeated four or five times; finally wash in water, the excess of which is removed with a blotter, dry the film, and mount in balsam. Pappenheim claims that by this method smegma bacilli do not retain the red dye but are stained blue. Sections may be stained with carbol-fuchsin and differentiated by Gabbet's method, or decolorization may be accomplished by using a twenty-five per cent. aqueous solution of nitric or sulphuric acid followed by sixty per cent. alcohol and water; after the acid has been fully removed by the alcohol and water the tissue cells can be stained in one per cent. methylene-blue for five

[1] "Berl. klin. Woch.," 1898, p. 809.

[2] This substance is also called rosolic acid, and I believe is identical with aurin.

minutes, followed by water, dehydration with alcohol, and clearing in xylol, cedar oil, or oil of cloves. The clove oil tends to carry differentiation too far, and the specimens do not keep well unless it has been thoroughly removed by xylol or cedar oil before mounting in balsam. As the bacilli may be scanty in urine and pathologic exudates, sedimentation is important and a number of spreads should be examined. As there are numerous acid-fast[1] bacilli resembling more or less closely the tubercle bacillus, when results by staining methods are not satisfactory animals should be inoculated.

Agglutination.—The blood of tuberculous patients contains agglutinins for the bacillus, but the difficulty in securing and maintaining homogeneous cultures free from clumps, and the fact that our present knowledge of the reaction indicates that it is less constant and trustworthy than typhoid, have prevented its general adoption.[2]

Tuberculin consists of certain extracellular toxins of the tubercle bacillus and such endotoxins as are extracted by boiling glycerin-bouillon cultures of the organism. For its preparation luxuriant growths of the bacillus on glycerin bouillon, having attained their maximum development, are boiled, filtered through paper, and the filtrate concentrated to one-tenth the original volume; finally the fluid is filtered through porcelain. Tuberculin has been used for therapeutic purposes and for diagnosis, especially for the recognition of latent tuberculosis in bovines. Cattle are tested by the subcutaneous injection of 0.3 c.c. to 0.5 c.c. diluted in 10 c.c. of a 0.5 per cent. aqueous solution of carbolic acid. In man the dose should rarely exceed 0.5 c.c. In tuberculous animals, including man, injections of tuberculin are followed by a rise of temperature amounting to 1.5° C. to 3° C.

The cases of reported infection of man by the **bacillus of avian tuberculosis**[3] are not convincing; it is certain that the organism plays no important part in human pathology. The same is true of tubercle bacilli obtained from poikilothermic animals.[4] Members of both these groups have been used for immunizing lower animals and a few studies have been made on man; the results so far are not such as to arouse enthusiasm, although Trudeau and others have shown that by the use of bacillary products and the organisms themselves it is possible to influence the evolution of lesions resulting from more virulent organisms.

Pathogenesis.—Much discussion has arisen as to the identity of the tubercle bacilli obtained from warm-blooded animals. The controversy has been particularly heated with regard to bovine and human bacilli, and, while much may be said on both sides, I believe it is safe to conclude

[1] The term acid-fast is applied to organisms resisting decolorization by acids. A full review of these organisms will be found in a paper by Rosenberger, "Medicine," March, 1904; also "Publications from the Laboratories of the Jefferson Medical College Hospital," vol. i, 1904.

[2] See Rosenberger, "Publications from the Laboratories of the Jefferson Medical College Hospital," 1904, vol. i; also Arloing and Courmont, "Boston Med. and Surg. Jour.," 1904, vol. cli.

[3] An excellent review of this organism is given by Moore, "Jour. Med. Research," May, 1904, p. 521.

[4] For studies of the tubercle bacillus in cold-blooded animals see Dubard, "Revue de la Tuberculose," 1898, vol. vi, p. 13; Bataillon, Dubard and Terre, "Zeit. f. Tub.," 1902, vol. iii, p. 467; Sibley, "Trans. Path. Soc. of London," 1892, vol. xliii, pp. 189 and 426; Hansemann, "Centralbl. f. Bakt.," 1903, xxxiv, p. 212, also Friedmann, "Deut. med. Woch.," Jan. 28, 1904, No. 5, p. 166.

that they are closely related strains. Practically all warm-blooded animals may be infected with tubercle bacilli; some, however, are much more susceptible than others; the ass and the goat are much more resistant than the horse or cow. In man the disease is exceedingly prevalent. In Germany during 1894 diphtheria and croup, whooping-cough, scarlet fever, measles, and typhoid gave a total mortality of 116,705; tuberculosis, 123,904.

Susceptibility.—Mortuary statistics go to show that practically all adults have at some time harbored the tubercle bacillus. The fact that a large number escape the ravages produced by the organism clearly indicates that those who succumb must offer less resistance to the inroads of the infection than those who survive. Exactly what determines this increased susceptibility is not known. Children of tuberculous parents are clearly more susceptible than those having a healthy parentage. Overcrowding, bad sanitary conditions, and dust occupations undoubtedly favor the occurrence of the infection.

Paths of Infection.—*Prenatal Tuberculosis.*—Tubercle bacilli have been demonstrated in the semen of tuberculous animals, including man, and it is equally possible that the ovum might contain the bacilli; proof, however, of conceptional tuberculosis is not conclusive, although the possibility must be admitted. *Transplacental infection* has been produced experimentally in lower animals; Auchè and Chambrelent [1] have been able to find twenty reported instances in which infection took place through the human placenta, which, whenever examined, has been found infected. [2]

Inoculation tuberculosis is seen in the postmortem nodule, *verruca necrogenica* of Wilks. The author has had an opportunity to observe a rather extensive local tuberculosis of the tendon-sheaths of the hand and wrist, resulting from infection of an open wound upon the thumb; the patient had nursed a son suffering from pulmonary tuberculosis, and during his illness had accidentally wounded her thumb. The wound was slow to heal, and even before its disappearance tuberculosis of the adjacent tendon-sheath developed; later the infection extended to a number of tendons in the wrist, eventually following the course of these structures in both the dorsal and palmar tissues. Ware[3] has been able to collect 21 cases of inoculation tuberculosis following ritual circumcision, and Bruns [4] reported four instances of cutaneous inoculation by the hypodermic needle. Ravenel [5] has collected the recorded instances of inoculation of man by bovine bacilli.

Inhalation Infection.—It is the consensus of opinion that tubercle bacilli most commonly enter the system with the inhaled air; in this way infection may reach the nose, tonsils, pharynx, larynx, trachea, bronchi, and lungs. Infection through the nasal mucosa must be rare; oral and laryngeal infection will be again referred to when discussing food infection. Kingsford,[6] studying tuberculosis in children, thought that 49 per cent. of his patients were infected through the

[1] "Arch. de Med. Exp.," 1889, xi, p. 521.
[2] See Giepel, "Münch. med. Woch.," Sept. 20, 1904, p. 1676, on "Tuberculosis of the Human Placenta."
[3] "N. Y. Med. Jour.," Feb. 26, 1898.
[4] "Münch. med. Woch.," Sept. 13, 1904.
[5] "Proc. Path. Soc. of Phila.," May, 1902, p. 18.
[6] "Lancet," Sept. 24, 1904, p. 889.

mucosa of the trachea or larger bronchi. Anatomic studies indicate that the pulmonary tissues are more commonly affected in this way than are the larger bronchi, trachea, or larynx.

Ingestion Tuberculosis.—Inhaled tubercle bacilli must frequently be deposited upon the oral and pharyngeal mucosa and on the tonsil, and to these must be added organisms entering with the food. There can be no doubt that bacilli may reach the cervical lymph nodes from lesions in the mouth or from the tonsils and pharynx. The frequency with which tuberculosis attacks the cervical lymph-nodes, particularly in childhood and adolescents, argues strongly for this path of infection. Kingsford[1] from the tonsils of 17 children found evidence of tuberculosis in 7, although in only one of these was there reason to believe that the tonsillar lesion might be primary. Infection through the esophagus and stomach is rare. With regards to the frequency of intestinal infection there has been, within recent years, the warmest controversy. Certainly primary intestinal tuberculosis is rare. Behring[2] strongly contends for infection through the intestine, holding that it is not necessary to prove a primary lesion of the mucosa, although this may have been present. Ravenel,[3] Dobroklonski,[4] and Bisanti and Pansiet[5] have shown that in animals tubercle bacilli may pass through an intestinal mucosa in which there is no demonstrable lesion.[6]

Morbid Anatomy of Tuberculosis.—In order that the tubercle bacillus may produce its characteristic lesions the organism must pass the epithelial barriers and enter the connective tissues. The exception to this general statement is found when the organism colonizes on epithelial surfaces, for example, the mucosa of the middle ear, the pulmonary air vesicles, or in the Fallopian tubes. When growing in such locations, the bacillary products promptly incite a reactive inflammation accompanied by accumulation of the leukocytes, necrosis of the overlying epithelium, and caseous changes in the exudate. Unless promptly circumscribed the extending necrosis exposes the connective tissue into which the bacillus enters, giving rise to a characteristic lesion—the **histologic tubercle.** This structure—ordinarily called a **miliary tubercle**—is primarily an accumulation of cells derived largely from the blood and adjacent lymph-spaces.[7] The tubercle bacillus both dead and living exerts a strong chemiotactic power on the mononuclear leukocytes; deposited in the tissues, an accumulation of these cells rapidly forms around the organism. There soon appear in the mass, cells much larger than the lymphoid elements, about the origin of which there is less certainty. Some hold that they are derived from mononuclear leukocytes, others from the endothelium of the blood-vessels, or from the connective-tissue cells. It is probable that they

[1] "Lancet," Jan. 9, 1904, p. 89.

[2] For recent papers supporting Behring's views see Beitzke, "Berl. klin. Woch.," Jan. 9, 1905.

[3] "Jour. Med. Research," Dec., 1903, p. 460.

[4] "Arch. de med. Exp.," March 1, 1890, p. 253.

[5] "Soc. de Biol.," Jan. 28, 1905.

[6] For further discussion of infection paths in tuberculosis see Wassermann, "Berl. klin. Woch.," Nov. 28, 1904; Bartel, "Wien. klin. Woch.," April 14, 1904; and Fischer, "Münch. med. Woch.," Aug. 23, 1904.

[7] See Miller, "Jour. of Path. and Bact.," November, 1904, vol. x, p. 1, on "Histogenesis of the Tubercle."

are of leukocytic origin. Near the center of the young tubercle, giant cells are the next conspicuous structures observed. These vary in size, but may attain a maximum diameter of 75 μ. In the typical cell of this kind the remaining nuclei are peripherally distributed and the center of the cell granular, while from its margin spiculated extensions project among the adjacent cells. By appropriate methods tubercle bacilli in varying numbers can be found in its interior. With regard to the origin of these structures, two views are held: (1) They result from confluence of the epithelioid cells and increase in size by the continued merging of these elements. (2) It is not impossible that some of the giant cells are derived from proliferated endothelial or fixed connective-tissue cells, in which the nuclei have divided without division of the protoplasm. Miller is strongly inclined to the origin first suggested. Within the developing tubercle there is usually demonstrable a reticulum which is more conspicuous in some places than in others. Miller believes that it represents prolongations of connections between the original cells of the tubercle,—a view long ago advanced by Rindfleisch, and which best explains its general characters. It is possible that part of the reticulum is residual connective tissue that has not, as yet, disappeared under the influence of the bacillary toxins. With regard to the noncellular constituents of the tubercle, fewer accurate data are obtainable. In young tubercles it may be possible to demonstrate the presence of fibrin, and this is usually considered an evidence of coagulation necrosis.

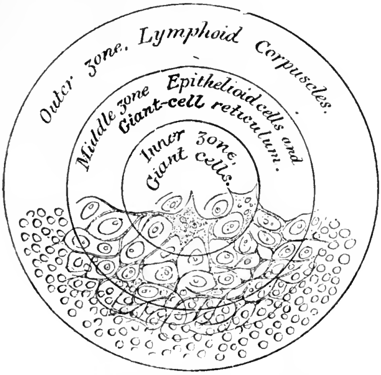


FIG. 83.—DIAGRAM OF THE STRUCTURE OF A TUBERCLE; A PURELY THEORETIC IDEA, RARELY DEMONSTRATED.—(*Gould.*)

The mass just described varies in size, being rarely larger than a pinpoint (one or two millimeters), although it may be much larger; as a rule, a number of these develop conjointly, and become confluent. The tubercle large enough to be seen by the unaided eye contains, as a rule, many small tubercles, such as that described. By the changes already noted, the capillary blood-supply is cut off from the center, favoring the occurrence of necrotic and degenerative processes brought about by the specific action of the bacillus, or, more properly, of the bacillary products. Coagulation necrosis terminates in solidification of any liquid exudate the product of which, with the dead cells, proceeds to caseation. In the beginning of this process granular and fatty changes occur in the cell protoplasm, the cell outlines become indistinct or disappear, and the nuclei shrivel and disintegrate; the nuclear fragments often retain their affinity for basic dyes long after the structurally perfect cell has disappeared. The caseous area produced by the foregoing changes may follow the peripheral extension of the process until two or more tubercles join by confluence into the formation of a single mass. Caseation may be accompanied by liquefaction, coagulation, or hyaline necrosis; eventually, the mass is converted into

a yellowish nodule of structureless detritus, the so-called **yellow tubercle**; prior to the stage of softening the mass was referred to as a **gray tubercle**; where a number of these run together, the collection shows a decided tendency to evacuate itself by discharge through the most feasible route, leaving behind a cavity or ulcer. If not in all, certainly in a large percentage of the cases, dissolution of the tubercle is brought about through a secondary infection by the organisms of suppuration. The tuberculous ulcer and abscess are more commonly, particularly in the respiratory organs, hastened to their full development by the added pyogenic invasion. This terminates the process of softening, and is an unfavorable ending of the tuberculous lesion.

Cured and Healed-in, Latent, or Quiescent Tuberculosis.—Grancher[1] found that in 896 children, 141 manifested unmistakable evidence of

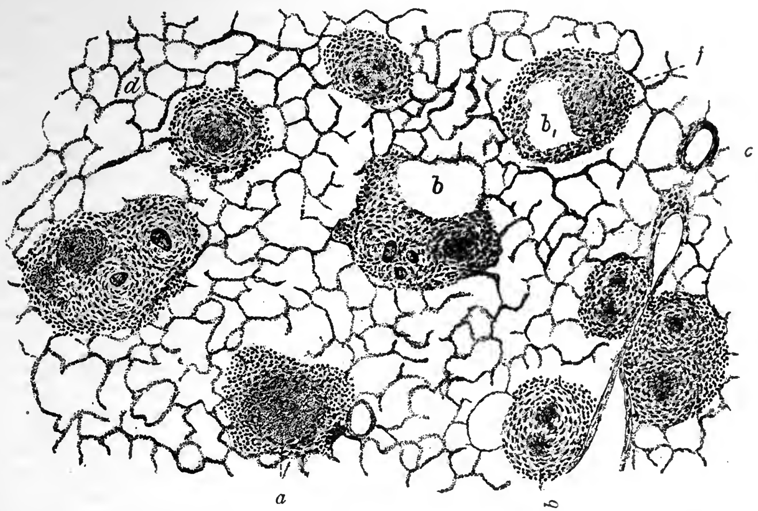


FIG. 84.—ACUTE DISSEMINATED TUBERCULOSIS OF THE LUNG.—(*Schmaus.*) ×40 diameters.

a. Tubercle undergoing caseation. Just below the letter *b* are two tubercles: the one on the left contains three giant-cells; the one on the right shows beginning caseation. b_1, b_1. Tubercles. *c*. Nodule containing at least four tubercles; two show beginning caseation and two contain giant-cells. *d*. Alveolus. To the left of *e* is a blood-vessel. *f*. Area of beginning caseation. Other tubercles are also shown.

latent ganglio-pulmonary tuberculosis. Mortuary statistics by careful observers show that a careful postmortem examination reveals evidences of healed-in or cicatrized tuberculous lesions in from eighty-five to ninety per cent. of all cadavers examined. In most cases the tuberculous nodule is of the caseous, calcareocaseous, or fibrocaseous type; less commonly it is fibrous. There can be no doubt that tuberculous inflammation of the peritoneum, pleura, and meninges may completely recover, often leaving no healed-in or latent area of quiescent infection. When colonization of the bacillus is widely disseminated in an organ the process is rarely arrested, but even extensive infiltration is sometimes suppressed; with Prof. Hearn and Dr. Thornton, at operation, I saw a case of tuberculous peritonitis the bacterial nature of which was estab-

[1] "Bull. de l'Acad. de Med. Paris," lxviii, No. 25.

lished by examination of excised portions; beneath the hepatic capsule, wherever the liver was exposed, innumerable tubercles were present; the patient, however, made an eventual recovery. Spengler[1] reports an instance of healed miliary tuberculosis of the lungs. These organs contained numerous small, dense nodules of scar tissue, a few necrotic foci, but neither giant cells nor bacilli. The common impression that tuberculosis is an incurable disease has long been shown to be incorrect, and it is now generally accepted that a very large percentage of the infected fully recover. When recovery does not take place, there is not infrequently more or less successful effort at local limitation of the infection. In favorable cases this is brought about by the production of a dense wall, through which any fluid that results from the degenerative changes may be partly absorbed, leaving behind the caseous detritus, containing not uncommonly tubercle bacilli; into the fibroid capsule and caseous material calcareous infiltration may occur, forming a stone-like mass, in which the tuberculosis virus may be destroyed or indefinitely stored. Sometimes the fibroid change (*fibrosis*) may be conspicuous and the calcareous infiltration but slight; in other instances the calcific matter may obscure the whole mass. The tubercle bacilli contained within such nodules may retain their viability, and hence their pathogenicity, or, in the course of time, may be no longer demonstrable. At first the organism stains with its characteristic activity—a reaction that becomes less and less manifest, and eventually disappears, so that, in old tubercles, under suitable conditions, the organism may be destroyed, or at least not demonstrable, and the degenerated contents of the mass may be no longer infective. During the later stages in the development of this body it is known as a **quiescent tubercle** or tuberculous area. Such "healed-in" tubercles may remain inactive or may, if they contain viable bacilli, manifest recrudescence. The length of time during which the bacilli retain their pathogenic activity can never be foretold; therefore, a quiescent tuberculous area must always constitute a menace to health, as, under favorable conditions, the bacilli may at any time be rapidly disseminated, giving rise to miliary tuberculosis.

Other Anatomic Divisions of Tuberculosis.—When the infection is restricted to a small area, it is called *localized tuberculosis*. If miliary tubercles are scattered through an organ, the condition is one of miliary tuberculosis of the organ involved; for example, miliary tuberculosis of the lung, miliary tuberculosis of the liver, etc. If the bacilli have been widely distributed through the body, many organs containing characteristic tubercles, the condition is called general *miliary tuberculosis*. *Chronic caseous tuberculosis* is that form in which confluence of tubercles and extensive caseation give rise to cheesy masses which may be large or small. When such caseous areas discharge their contents on the surface or into one of the body-passages communicating with the exterior and permitting escape of the cheesy material, the term *chronic ulcerative tuberculosis* is used. The last is the form frequently present in the lung, where it gives rise to excavations called *cavities*. In some cases the evolution of the disease is associated with the production of a large amount of fibrous tissue,—a condition called *chronic fibroid tuberculosis*. A less frequent type of tuberculous infection, involv-

[1] "Zeit. f. Hyg. u. Infectkrank.," 1904, xlvii, p. 133.

ing particularly the intestine in the neighborhood of the ileocecal valve, but also occurring in the larynx and on the serous membranes, is known as *chronic hyperplastic tuberculosis*.[1] In this form a large amount of fibrous tissue is produced often without any caseation and containing but few tubercle bacilli. The enormous increase in fibrous tissue is shown by the fact that the intestinal wall may be 1 cm. or even 2 cm. in thickness. Stenosis of the larynx, intestine, or other tube may result from the formation of such masses. Surgeons have found that this type of tuberculosis yields to treatment by excision, which often results in a cure. Histologically the tissue is composed of fibrous and fibro-hyaline-elements containing perivascular accumulations of lymphoid cells; giant cells are frequently absent and tubercle bacilli scanty and difficult to demonstrate.

The name *tuberculoma* has been applied to more or less perfectly circumscribed masses of granulation and hyaline fibrous tissue often possessing a structure closely resembling the gumma of syphilis. I believe that this form of tuberculosis is nothing more than a nodular type of the hyperplastic lesion. The histology of the two conditions is strikingly similar. Tuberculomas are found particularly in the larynx, but are occasionally encountered beneath the nasal mucosa and sometimes in the viscera. I have seen such a nodule in the heart, although in that location they are rare. Some writers speak of chronic caseous collections as tuberculomata; the term, however, should be restricted to the type of lesion just described.

Secondary Infection in Tuberculosis.—In ordinary forms of tuberculosis the symptoms are largely due to pyogenic infection of tuberculous areas; this is especially true of chronic caseating lesions associated with the formation of cavities or ulcers. The character of the infection has been especially investigated by Sata,[2] Ophüls,[3] Weismayr,[4] Oestern,[5] Petroff,[6] and Bruns[7]; the organisms chiefly found have been the white and yellow staphylococci and, in the lungs, streptococci, pneumococci, influenza bacilli, tetracocci, and less commonly mould fungi. By the introduction of additional bacteria, tissue necrosis is rapidly extended and the systemic poisoning produced by the absorption of microbic poisons proportionately increased. Under suitable conditions saprophytic organisms may infiltrate the necrosing tissues, hastening liquefaction and adding their quota of absorbable toxins.

Extension of Tuberculosis.—Tuberculosis develops as an initial lesion, inoculation, or point of primary invasion, from which local or general extension may occur. The necessity of a recognizable initial lesion is not always to be insisted upon, for when a guinea-pig is fed tubercle bacilli, infection of the lymph-nodes of the mesentery may occur without any recognizable focus in the alimentary canal. Tuberculosis of the mesenteric nodes, as seen in children, is similarly explained, particularly when we take into consideration the frequency with which milk contains tubercle bacilli. The local tuberculous lesion seen in the

[1] See Tuberculosis of the Intestine.
[2] "Ziegler's Beiträge," 1899, Supplement.
[3] "Amer. Jour. Med. Sci.," 1900.
[4] "Zeit. f. Heilk.," Bd. xxii, 1901.
[5] "Centralbl. f. Bakt.," xxxvii, review of literature and original observations.
[6] "Ann. de l'Inst. Pasteur," Aug. 25, 1904.
[7] "Deut. Zeit. f. Chir.," 1904, Bd. lxxv.

lymph-nodes of the neck must have resulted from infection through the oral cavity, possibly the tonsil, without there having been any history to indicate a past or associated initial lesion of the mucous membranes at the point of ingress. The possibility, however, of superficial initial lesions has already been pointed out. (See p. 148.) Tubercle bacilli may enter the body without the production of any recognizable superficial lesion. The occurrence of tuberculosis of the body of a vertebra, or of primary tuberculosis of a joint, without other evidences of the disease, indicates such a possibility. The fact that a local lesion is not produced, and that bacilli may apparently pass into, and travel by, the circulation, eventually inducing tuberculosis in distant parts, indicates that the induction of a primary tuberculous nidus is dependent upon factors other than the mere presence of tubercle bacilli. These factors are probably the lessened resistance of certain tissues, or, we might say, greater susceptibility, and the occurrence of points of least resistance. The latter may be produced by associated lesions or by injury. The fact that certain tissues possess a higher degree of susceptibility to tuberculosis is indicated by the frequency with which the disease occurs in the lungs, bone, and lymph-nodes. The presence of such heightened susceptibility also indicates a relative immunity in other tissues: for example, the muscles, in which typical tuberculous lesions are rare. From the initial or primary lesion propagation may occur by one of the following routes:

1. *By the Blood.*—The wide-spread dissemination of tubercles necessarily implies that the organisms have been transported by the circulating blood.[1] The initial lesion from which the bacilli are poured into the circulation may be a tuberculous endangeitis (*endophlebitis* or *endarteritis tuberculosa*) due to the production of a cheesy nodule in the vessel wall, probably through infection by the vasa vasorum. In other cases the bacilli may be implanted directly on the intima, or, less commonly, on the endocardium including the valve leaflets. Growing in such locations, hematogenous dissemination is to be expected. The initial lesion may be in the *thoracic duct*, which can be infected by bacilli traversing its lumen or from mesenteric, retroperitoneal, or mediastinal lymph-nodes, either by drainage from these structures or by erosion of a caseous node through the duct. A *caseous lymph-node* in the lung or elsewhere or a primary focus in bone may discharge its contents into a vein, or, less commonly, an artery. In a study of 123 cases of acute miliary tuberculosis Schmorl found that the largest percentage arose from erosion of vessels by contiguous caseous lymph-nodes; in 5 cases he observed tuberculous nodules in atheromatous ulcers. Tubercle bacilli may be present in the circulation in sufficient numbers to be demonstrated in drawn blood, constituting a true *tuberculous bacillemia* or *septicemia*.

Dissemination of tubercle bacilli by means of the blood usually results in the wide-spread distribution of the germ, followed by an eruption of numerous tubercles in various organs. Such a condition is called *general*

[1] See recent papers by Benda, "Berl. klin. Woch.," 1899, Nos. 26, 27, and 29; Landsteiner and Mucha, "Centralbl. f. allg. Path. u. path. Anat.," Sept. 30, 1904; Silbergleit, "Virch. Arch.," Feb. 1, 1905, Bd. 179, p. 283; and Forssner, "Centralbl. f. allg. Path. u. path. Anat.," 1905, Bd. xvi, No. 7. Longcope has recently reported dissemination secondary to tuberculosis of the thoracic duct; the paper will appear in the Report of the Ayer Clinical Laboratory of the Pennsylvania Hospital, vol. iii.

miliary tuberculosis and is associated with more or less marked febrile and other toxic phenomena. In such cases not only do the viscera suffer, but infection of one or more serous membranes, especially the meninges, is not infrequently present. The tubercles rarely attain any considerable size, as the patient usually dies before sufficient time has elapsed. In other instances the amount of infectious material disseminated was evidently small, giving rise only to a few tubercles scattered here and there through the viscera. Under such circumstances the patient may survive long enough for the tubercles to attain considerable size, and even to caseate. Whenever there is a general miliary tuberculosis such as just indicated, there is reason to believe that a primary caseous nodule has communicated in some way with the general circulation. Often a most careful postmortem will fail to show the primary lesion. The author recalls a case of general miliary tuberculosis involving nearly all the viscera, in which a most thorough search was about to be abandoned when the primary nodule was discovered in the anterior part of the body of a dorsal vertebra. Subsequent inquiry elicited the fact that the patient had, a few weeks before admission to the hospital, encountered a severe fall, which strained his back, and to which he attributed his illness. The slight inflammatory changes that surrounded the nodule indicated that possibly, indeed probably, the injury had caused the caseous area to break into the surrounding cancellous bone and favored the dissemination of the contained infectious matter. The possibility of disseminating tubercle through the blood-stream as the result of incomplete operative procedure has been pointed out by many surgeons. The breaking up of a tuberculous area, without at the same time completely eradicating infection, may be followed by general dissemination of the poison, miliary tuberculosis, and death.

2. Another means of extension is by the *lymph-stream.* This is manifested in the tuberculous lymph-nodes of the neck in children, which result from infection through the tonsils and through diseases of the teeth, gums, and oral mucosa; the same type of dissemination is shown by the occurrence of tuberculous processes in the structures along the course of the lymph-stream in tuberculous ulceration of the intestine. Infection from the thoracic duct, referred to above, might with propriety be included with this group.

3. In addition to the lymph and blood, the bacilli may follow the *course of other fluids.* Thus, tuberculosis of the alimentary canal may be secondary to tuberculosis of the respiratory passages, and may be due to swallowing bacilli-laden sputum; tuberculosis of the bladder or tuberculous abscess of the perineum may be secondary to tuberculosis of the kidney.

4. Locally, tuberculosis may spread by *continuity* or *contiguity* of tissue; this may occur even against the ordinary course of fluid currents, as in tuberculosis of the ureter, which may be secondary to tuberculosis of the bladder; tuberculosis of the prostate may be secondary to tuberculous processes in the rectum or in other contiguous structures; tuberculosis of the intracranial tissues may be due to extension of tuberculosis from the middle or internal ear, mastoid cells, or frontal sinuses.

Site of Tuberculosis.—One of the most common points of infection is the lung; following this in frequency, tuberculous affections of the joints,

bones, and lymph-nodes are next in order; these are followed by tuberculosis of the mucous membranes other than the lungs, tuberculosis of the serous membranes. tuberculosis of the skin, tuberculosis of the spleen, tuberculosis of the liver, tuberculosis of the brain, tuberculosis of the generative organs, and tuberculosis of the heart and voluntary muscles, in about the order given.

Tuberculosis of the organs is further considered in Part III. The only form of local tuberculosis that will be described at this point is lupus.

Tuberculosis of the Skin (Lupus).[1]—This condition usually begins as a lymphoid infiltration following the course of the vascular loops in the corium. The process slowly extends by the development of outlying tubercles that coalesce with the older nodules. The fully formed tubercle in lupus may be, and indeed usually is, structurally identical with tubercles seen elsewhere. Sometimes the miliary tubercle in the skin is quite atypical, and in the absence of the bacilli a satisfactory diagnosis can not be made. In the ulcerative form of lupus (**lupus exedens**) the coalescence of tubercles in the corium, and even for some distance in the subcutaneous tissue, associated with the obliterative changes in the capillaries followed by caseation, leads to necrosis of the overlying derma and the formation of an ulcer. Occasionally, superficial necrosis does not occur, and hence ulceration is absent. In such cases the infiltration commonly shows more fibrous tissue than in the ulcerative form of the lesion; the skin is slightly raised, and is usually somewhat more adherent than normal; occasionally, outlines of caseous masses can be detected beneath, even when superficial necrosis does not follow. This form of cutaneous tuberculosis is known as **lupus nonexedens.** It is probable that cutaneous tuberculosis results from local inoculation; the author has seen one well-marked and protracted case of lupus that followed vaccination, and two cases of extensive cutaneous tuberculosis in which the lesions followed the application of the actual cautery, the ulcerative process having been purposely prolonged for its so-called alterative action. Lupus is a particularly chronic and intractable disease, and may be associated with, or followed by, more general tuberculous dissemination.

Pseudo-tuberculosis[2] includes a number of, probably many, infectious processes, usually subacute or chronic, characterized by the production of tubercles which macroscopically and microscopically may be almost, if not quite, indistinguishable from similar structures resulting from infection by the tubercle bacillus. A large number of organisms entering the tissue in man and certain lower animals are endowed with this property. Not only do such germs produce tubercles, but often the morphology and stain reaction of the microbe so closely resemble the tubercle bacillus that differentiation becomes extremely difficult. Cer-

[1] For recent papers on tuberculosis of the skin see Hartzell, "Amer. Med.," July 2, 1904, also Juliusberg, "Mittheilungen a. d. Grenzegebieten d. Med. u. Chir.," 1904, Bd. 13, Heft 4 and 5.

[2] See works referred to in foot-note, p. 81. The earlier literature will be found in Muir's article, "Jour. of Path. and Bact.," May, 1898, and Flexner, "Jour. Exper. Med.," vol. iii, 1898. More recent papers may be traced from the articles by Sanfelice, "Centralbl. f. Bakt.," Bd. xxxviii, Jan. 25, 1905, p. 30; Citron, "Zeit f. Hyg. u. Infektkrank.," 1905, Bd. 49; Vincenzi," Gazette degli Osped. e delle Clin.," 1904; Koehler and Hall, "Jour. of Cutaneous Dis.," Dec., 1904.

tain animal parasites (worms and ova) may produce pulmonary lesions not unlike those of tuberculosis. Of the vegetable parasites endowed with this quality special mention should be made of the organisms isolated from butter and milk by Rabinowitsch, Horn, Möller, and others, and the organisms found in grass by Möller, in sewage by Houston, in earth by Karlinski, and in manure by Möller, and others. A number of these organisms injected into the lower animals give rise to nodules possessing the histology of similar structures produced by the tubercle bacillus. The lesions resulting from infection by some of the saccharomyces may also resemble tuberculosis. Exactly how common these processes are in man is not known, but it is highly probable that many cases of atypical or irregular tuberculosis, if carefully studied, would be found to be instances of pseudotuberculosis and could probably be traced to a yeast, mould, or bacterium other than the tubercle bacillus.

Leprosy[1] is an extremely refractory, chronic infectious disease communicable under certain conditions and due to the **Bacillus lepræ** (Hansen). The organism resembles the bacillus of tuberculosis both in morphology and stain reaction. It is non-motile and measures 3 μ to 6 μ in length and 0.6 μ in thickness. Several observers have reported the successful cultivation of Bacillus lepræ; most claims have not been generally accepted. Emile-Weil, by transplanting portions of rapidly growing, fresh nodules from tuberculous leprosy, obtained pure cultures of the organism, growth persisting from fifteen to twenty-five days; transplantation from the initial cultures yielded negative results. Clegg's results seem conclusive; this observer obtained initial growths of Bacillus lepræ in symbiosis with amebæ and cholera vibrios; transplantation was successful, and finally, by subjecting the mixed cultures to thirty minutes at 60° C., the symbiotic parasites were killed and the bacillus of leprosy obtained in pure culture. Bacilli so obtained could be grown on ordinary laboratory media. Prof. Duval has verified Clegg's observations. Rost's report of successful cultivation on sodium-chloride-free media has not been verified by other experimenters.

Demonstration.—The bacillus of leprosy can be colored by the same methods used for demonstrating the tubercle bacillus and also by ordinary aqueous solutions of anilin dyes. The organism is Gram-positive. For demonstrating the presence of the bacillus in tissues small fragments are macerated in a glass mortar with a few drops of normal salt solution and the resulting tissue emulsion spread on cover-glasses, dried, fixed, and stained as directed for tubercle bacilli. When excised tissues can not be obtained the leprous nodule may be squeezed between the blades of a forceps, punctured with a large needle or a small knife,

[1] See works referred to in foot-note, p. 81. Nicolle, "Acad. des Sci.," Feb. 20 and 27, 1905, "La Presse Méd.," March 1, 1905, p. 134, "La Sem. Méd.," March 8, 1905, p. 116. McDonald, "Jour. Amer. Med. Assoc.," June 6, 1903, p. 1567. Thompson, "Report of the Board of Health on Leprosy in New South Wales for the year 1903." Emile-Weil, "Ann. d. l'Inst. Pasteur," Dec., 1905. Clegg, "Philippine Jour. of Sci.; B. Med. Sci., Dec., 1909. Rudolf, "Medicine," March, 1905, p. 175; Tonkin, "Brit. Med. Jour.," Sept. 17, 1904. Ormsby, "Jour. Amer. Med. Assoc.," Dec. 31, 1904. Sukurane, "Centralbl. f. allg. Path. u. path. Anat.," 1903, Bd. xiv, p. 110. Jeanselme, "La Presse Méd.," Sept. 21, 1904, p. 601. Doredorf, "Annales of Otol., Laryngol., and Rhinol.," June, 1904. In addition to the foregoing, good studies of leprosy will be found in the reports of the various congresses devoted to the subject.

and the expressed juice spread on covers and stained. The bacilli are often found in clumps or irregular masses, or within the so-called lepra cells, especially in properly fixed and stained sections prepared from excised tissues or in smears from the nose. Beaded and granular forms are usually present. The organisms are rarely found in the circulating blood, although post-mortem they may be demonstrated in the organs.

Pathogenesis.—Leprosy as a disease is restricted to man. By inoculation, Nicolle has succeeded in producing a typical leprous nodule in the *Macacus simensis*. The tissues removed from two inoculated animals contained bacilli identical with those found in the original lesion, and the structure of the nodule produced was essentially similar to that of the nodules found in man. With regard to the propagation of the disease we are indifferently enlightened. It is feebly contagious and in susceptible individuals easily inoculated. Jonathan Hutchinson's belief in a fish diet as a predisposing factor—if not actually the cause—has not been received with general approbation. The period of incubation is in some cases longer than that of any other disease of which we have accurate knowledge. Cases of leprosy have been reported in which the first symptoms appeared two or three decades after exposure to infection. Leprosy occurs in two chief clinical forms, although both of these may be present in a single case.

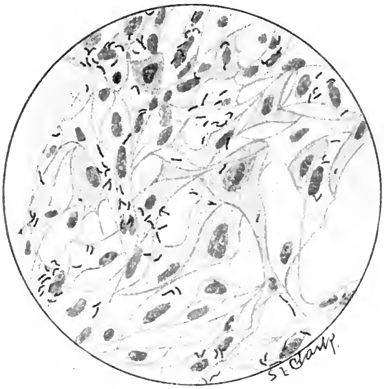


FIG. 85.—BACILLUS LEPRÆ (EXTRACELLULAR).

Anesthetic, smooth, or **trophoneurotic leprosy** involves the nerves, skin, bones, and viscera. The nerves most commonly affected are the ulnar, median, radial, musculospiral, intercostohumeral, external cutaneous, posterior tibial, and peroneal. The nerve affected is red, swollen, and rounded in shape; later it becomes harder, pale and grayish in color, with nodular or fusiform enlargements. Microscopically, the neurilemma may or may not be changed; in most cases, however, it becomes thickened, fibrous, and infiltrated with granule cells (lepra cells and lymphoid cells). Cicatrization and contraction may arrest function and eventually destroy the diseased nerve. The nerve lesion of leprosy begins as a perineuritis; the later degenerative changes are apparently due to the pressure upon the nerve and to interference with nutrition. Occasionally, the central nervous system shows some edema, and there may be an excess of fluid in the ventricles and in the subarachnoid space. The larger nerve-trunks are likely to show some fibroid hyperplasia, with slight atrophy; the cutaneous nerves are degenerated, hence the skin is anesthetic; the hair-bulbs, the sweat-glands, and the sebaceous glands are atrophied and fibroid. The eruptions of leprosy assume a number of forms. They are sometimes erythematous; frequently attended by pigmentation, and at other times by reduction in the normal pigment. In purely anesthetic leprosy the maculæ are never elevated until late in the disease. As a result

PLATE I.

FIG. 1.—BACILLUS LEPRÆ.
Culture of Bacillus lepræ with Entamœba coli. (From photomicrograph, through the courtesy of Prof. Duval.)

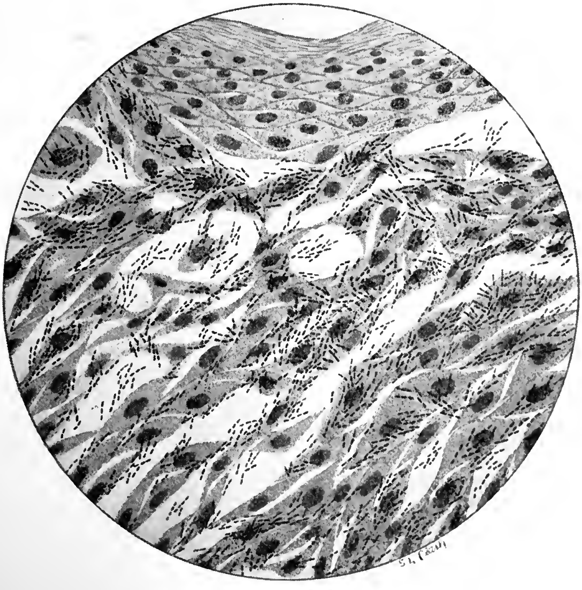


FIG. 2.—BACILLUS LEPRÆ.
Section of leprous nodule in skin.

of the trophoneurotic disturbance, muscular contractures occur; these may be followed by, or associated with, a varying quantity of muscle atrophy. The fact that the patient feels no pain as a result of injury of the affected part tends to increase the danger from this source. I have seen a case of leprosy in which the patient, a pipe-smoker, had burned off the ends of his fingers by pressing the tobacco down into his pipe. Necrosis and caries of the long bones have been observed.

Tubercular or Nodular Leprosy.—With infection of the skin or mucous membranes, preceded by the so-called prodromal eruptions, typical leprous tubercles are developed; "they may be flat or prominent, oblong or round, isolated or confluent, and in color varying from pale violet to dark brown; . . . . they are generally soft, but may be hard" (Danielssen and Boeck). These tubercles occur anywhere on the body, with the exception of the scalp; they are also rare in the palms of the hands and on the soles of the feet. Microscopically, each tubercle is made up of granulomatous tissue, composed of lymphoid and epithelioid cells retained in a loose connective-tissue matrix; in these masses the bacilli abound, both between and in the cells. Liquefaction necrosis occurs, followed by infection with pyogenic organisms, terminating in ulceration; such ulcers often heal rapidly; others, by extension, may give rise to large sloughing areas; the nodules occur also on the mucous membranes, particularly those of the nose and larynx. The bacilli may invade the viscera—lung, liver, spleen, and kidneys—in which they occasionally give rise to leprous nodules.

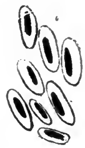


Fig. 86.—Bacillus of Rhinoscleroma. × 1400 diameters.

Mixed forms of leprosy are not uncommonly seen, both the anesthetic and the tubercular types being present. In other cases an attack of the anesthetic form terminates in the tubercular, or a patient having the tubercular type develops evidences of extensive anesthesia. It is held by many observers that the so-called mixed form is not truly a variety of leprosy, but is the ideal, complete, fully developed disease, and that the anesthetic and nodular types are incompletely evolved forms. *Lepra mutilans* and the so-called *gangrenous leprosy* are inappropriate names intended to describe the conditions rather than the disease. Leprosy may be complicated by the occurrence of other processes; tuberculosis is frequent, and inflammations of the kidney, septicemia, pyemia, extensive intestinal ulceration, amyloid disease, etc., are frequent associated lesions.

Rhinoscleroma[1] is an affection characterized by thickening and induration of the nasal submucosa, but occasionally involving the pharynx or larynx. The tumefaction usually begins in the nose; the affected areas are at first red or pink and very tender, later they become white. In these masses of granulation tissue numerous large round or oval cells (Mikulicz cell) containing many bacilli are constantly present, and the same organisms are found free in the lymph-spaces of the tissue. The rod-shaped, encapsulated germ (**Bacillus rhinoscleromatis**) closely resembles the bacillus of Friedländer, some believing that the two organisms are identical. It is stated that cultures of the bacillus of rhinoscleroma are a little more transparent, the nail-head surface growth slightly more gray, and the capsules persist longer in cultures on solid

[1] See works referred to in foot-note, p. 81.

media. The bacillus is not completely decolorized by Gram's method.

Glanders[1] is an infectious disease due to the **Bacillus mallei,** a rod-shaped, motile,[2] facultative anaerobic organism measuring $2\ \mu$ to $5\ \mu$ in length and $0.5\ \mu$ to $1\ \mu$ in breadth; ovoidal, pyriform, and swollen elements are found in most cultures, and sometimes long filaments are formed. Marx has described branching types, resembling the cladothrix or streptothrix. Some of the bacilli contain stained and unstained areas. The optimum temperature is 37° C., the minimum 25° C., maximum 42° C., and the thermal death-point between 55° C. and 60° C. It is not probable that the Bacillus mallei forms spores, although upon this point there is some doubt.

The glanders bacillus grows well on all the ordinary media, but glycerin-agar is especially adapted to the organism. The surface growth consists of a pale, white, moist, transparent, and slimy film, following the track of the inoculating needle; transverse striations are sometimes present. In bouillon, it produces turbidity followed by sedimentation. Potato cultures, at 37° C., are most characteristic; by the second day the bacillus gives rise to a thin, slightly yellowish, transparent layer, which in the course of a week takes a reddish-brown (chocolate or "café-au-lait") color with yellow or greenish-yellow tinging of the medium at the margin of the growth.

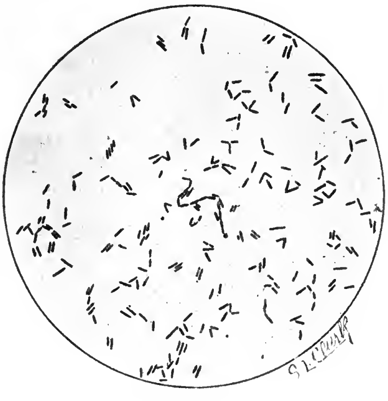


Fig. 87.—Bacillus mallei, Pure Culture.

Demonstration.—The Bacillus mallei requires prolonged staining with the usual anilin dyes, is easily decolorized, and Gram-negative. For diagnostic purposes the method of Strauss is commonly employed. A small fragment of infected tissue or a minute quantity of the culture thoroughly macerated in sterile water is injected into the peritoneal cavity of a male guinea-pig. Frothingham recommends that an ordinary swab, such as is used for diphtheria diagnosis (see page 118), be rubbed over the infected area and expressed in 3 c.c. of sterile water which is used for the injection. As the animal may die from associated pyogenic infection, more than one guinea-pig, preferably a number, should be injected. Within twenty-four to forty-eight hours foci of suppuration attack the peritoneal lining of the scrotal sac, forming adhesions to the testicle, which, later, also becomes involved. Usually both sides are affected, but to different degrees. Abscesses may develop along the needle track, and later inflammation of the nasal

[1] See references given in foot-note on p. 81. Frothingham, "Jour. Med. Research," Nov., 1901. Coleman and Ewing, "Jour. Med. Research," May, 1903, p. 223. Gutowski, "Arch. gen. de Med.," Sept. 1, 1903. Kleine, "Zeit. f. Hyg. u. Infectkrank.," 1903, Bd. 44, H. 2. Heanley, "Lancet," Feb. 6, 1904, p. 364. MacCallum, "Beitr. zur path. Anat.," 1902, Bd. xxxi, p. 440. Wherry, Bulletin No. 24, November, 1904, Biological Laboratories, Dept. of the Interior, Bureau of Government Laboratories.

[2] Motility is not a constant phenomenon, and some observers (Muir and Ritchie) deny its existence.

mucosa, joint swelling, and characteristic nodules may be found in the viscera. Gutowski recommends a modification of Mari's method, which consists in inoculating kittens which are killed at the expiration of forty-eight hours and cultures made upon agar from the spleen and blood.

Mallein is prepared in the same manner as tuberculin (see page 147) and for diagnostic purposes is used in the same manner. The maximum temperature rise is determined in from eight to eighteen hours, and should, for a positive diagnosis, exceed 1.5° C. A positive reaction is also manifested by more or less prostration and marked local swelling (12 cm. to 15 cm. in diameter), which does not subside for a week or more. Heanley does not think that confidence should be placed in the agglutination test, although animals may yield sera containing agglutinins for the bacillus.

Pathogenesis.—The Bacillus mallei is pathogenic for horses, asses, mules, sheep, goats, dogs, cats, lions, tigers, field-mice, and ground squirrels; cattle, white mice, rats, and birds are immune. The rabbit is refractory but susceptible.

Glanders in man occurs in two forms: (1) Localized, circumscribed, or chronic glanders, or farcy; (2) general, disseminated, acute, or septicemic glanders.

Localized Glanders.—Infection by the Bacillus mallei, involving the skin and adjacent lymph-glands, is called **farcy;** when the mucous membranes are affected, the condition is spoken of as glanders. At one time it was customary to describe acute and chronic glanders and acute and chronic farcy, but it is now recognized that glanders and farcy are due to the same cause, and that there is no essential difference between the pathology of the "farcy-bud" and the glanders nodule. By some the local or chronic manifestation of infection with the bacillus mallei is called glanders, while the term farcy is applied to the general, disseminated, acute, or septicemic glanders.

It does not seem probable that the organism can gain ingress except through an abraded or wounded surface, although experiments are not wanting to show that the bacillus may be forced into the skin when applied by inunction with even slight friction. As communicated to man, the disease usually is contracted from the horse, and is therefore most common in hostlers and those employed around stables, etc. When the glanders bacilli localize in the subcutaneous or submucous tissue, there develops a small nodule, rarely as large as a pea, made up of an almost pure leukocytic infiltrate, containing a few giant-cells and the characteristic bacilli. By necrosis, the nodule and adjacent mucous membrane or skin soften and disintegrate; the resulting ulcer is usually foul, without any abundant discharge; when a number of ulcers are located near one another, they not uncommonly show a decided disposition to become confluent, forming irregular serpiginous ulcers. There is likely to be lymphangitis extending to the neighboring lymph-nodes, which may become large and suppurate. This constitutes the so-called **chronic glanders** or **chronic farcy.** Chronic glanders not infrequently runs an extremely protracted course; von Baracz reported a case in which the disease lasted fifteen years, during which time it was wholly latent for an interval of five years.

Acute Glanders.—In the acute form the condition more closely resembles miliary tuberculosis in the rapid dissemination of the poison

and the wide-spread distribution of the lesions. Weichselbaum describes a case of acute glanders in which, without any apparent initial lesion, there occurred, throughout the viscera, multiple nodules, the character of which was not diagnosticated during life; at the postmortem a thrombus was found in one of the meningeal veins, and from this, no doubt, had arisen infected emboli, which had given rise to the general dissemination of the lesion. In this condition the bacilli are found in the blood and in the discharges; multiple cutaneous eruptions are likely to occur; the larger joints may be implicated, as in other forms of septicemia; in the male the testicles may be involved. Multiple abscesses may occur throughout the body, closely resembling pyemia. Death usually occurs from exhaustion. This constitutes the septicemic form of the disease, and may occur (1) without any initial lesion that can be discerned; (2) it may be associated with an initial lesion that runs a rapid course; (3) it may terminate the chronic form of farcy or glanders, as already described.

The secondary changes that may occur in a farcy nodule resemble in some respects those seen in tubercles. Latent or "healed-in" nodules are not infrequent; they commonly show peripheral fibrosis and calcareous infiltration similar to that already described when considering "healed-in" tubercles. (See p. 151.) Such latent masses are seen in lymph-nodes and in the lung, and occasionally in other viscera. During the development of the farcy node interstitial and peripheral hemorrhages are not infrequent, and in the lung an associated pneumonia is usually present. The latter may be restricted to a small zone around the node or it may, as in tuberculosis, involve a large area of the pulmonary tissue, giving rise to alterations that closely resemble those of croupous pneumonia. The routes of infection and dissemination are practically the same as those already given for tuberculosis. The occurrence of multiple abscesses scattered throughout the body, containing staphylococci as well as the specific organism of the disease, is indicative of the pyemic character of the lesion. The erythematous, papular, phlyctenular, bullous, and pustular eruptions, are also evidences of general infection; they have led to confusion in diagnosis, the disease having been mistaken for measles, chicken-pox, smallpox, syphilis, etc.

HYPHOMYCETES.

The **Hyphomycetes** or mould fungi consist of a branched, septate, filamentary meshwork composed of mycelium, from which arise hyphæ and conidia producing small, spheric, highly refractile bodies called spores. The special organs by which spores are produced are not always the same. Members of the higher group of moulds are easily identified, but as the scale is descended some of the special forms are not, with our present knowledge, readily classified. A number of the moulds are pathogenic for lower animals, but under ordinary conditions a few only give rise to disease in man.

Aspergillosis[1] is a morbid process induced by members of the

[1] Renon, "Etude sur l'Aspergillose chez les Animaux et chez l'homme," Paris, 1897. Bosin, "Centralbl. f. Bact.," xxxii, p. 589. Pearson and Ravenel, "Univ. of Penna. Med. Magazine," August, 1900. Ritter, "Prag. med. Woch.," Feb. 2, 1902. Cook, "Amer. Med.," Dec. 5, 1903. Elliott, "Ophthalmic Record," Nov., 1902, p. 582. Nakayama, "Zeit. f. Heilk.," 1903, Bd. xxiv, Abth. f. path. Anat., H. 4, p. 548. Birkett and Nicholls, "Montreal Med. Jour.," May, 1904.

aspergillus group. The **Aspergillus fumigatus, Aspergillus flavus,** and **Aspergillus niger** are the most important disease-producing species. They occasionally give rise to inflammation of the external and middle ear, and a definite form of *aspergillus keratitis* has been described. A most important morbid process produced by the parasite is **pneumo-aspergillosis,** which may be primary or secondary. It is probable that in a considerable percentage of cases the fungus is engrafted upon, and extends into, some previously existing pulmonary lesion. The disease is seen particularly in millers and in other persons handling grain, and in pigeon-feeders addicted to moistening seeds in the mouth. The Aspergillus fumigatus grows at a higher temperature (35° C. to 40° C.) than the niger (25° C.), which may account for the fact that the former is more commonly pathogenic. The pulmonary lesion produced by the fungus is essentially a pseudotuberculosis and may be acute or chronic. The bronchi are frequently dilated, cavities form, and in the chronic cases there is a notable interstitial pneumonia. Histologically the lesions consist of masses of leukcoytes, among which the mycelium of the fungus is widely distributed. There is usually marked bronchial thickening continuous with the increased connective tissue in the lung.

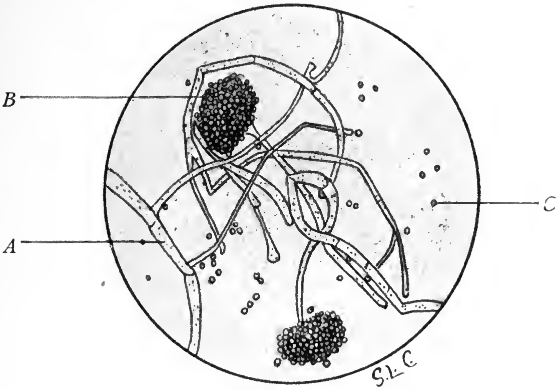


FIG. 88.—ASPERGILLUS.
A. Mycelium. *B*. Opened sporangium. *C*. Free spore.

It is not known that the members of this group produce a toxin, all experiments going to show that they do not; it has been claimed,[1] however, that pellagra is due to a toxic substance produced in maize by mould fungi, among which the aspergillus is thought to be active.

The **dermatomycoses**[2] are specific forms of cutaneous inflammation due to other members of the mould family. The most important of these are favus, herpes tonsurans (tinea tonsurans or barbers' itch), tinea versicolor (pityriasis, mycosis versicolor, or dermatomycosis furfuracea), and erythrasma.

Favus is usually restricted to the scalp, although Morris reported a case in which the lesion occurred on the scalp, trunk, and arms and also involved the finger-nails. Sulphur yellow crusts form about hairs which the mycelia and conidia penetrate; the underlying skin inflames, the hair sheds, and, as a result of inflammatory and atrophic changes in the bulbs, may not be reproduced. The parasite producing the

[1] Ceni and Besta, "Rivista sper. di Feniatria," 1904, vol. xxx, p. 865.

[2] Sabouraud, "Les Tricophyties Humaines," Paris, 1894. Bodin, "Les Champignons Parasites de l'homme," 1902. Bunch, "Lancet," Feb. 18, 1905. Minne, "An. de la Soc. de Med. de Fland.," 1904, lxxxiii.

lesion is the **Achorion schönleinii.** The spores of the thread penetrate the hair-follicle and may be found surrounding the bulb.

The organism is not difficult to grow, but on account of the large number of associated bacteria, isolation in pure culture is not easy; the extracted hair may be washed in sterile water and, by sterile instruments, divided into many fragments, of which inoculations may be made. Parts of the bulb are most likely to yield pure cultures. On agar the outlines are clear, the surface scaly, and in old growths cerebriform; the surface takes on a fine, whitish, powdery appearance. On gelatin, irregular, whitish, downy growths develop with slowly advancing liquefaction of the medium. The organism may be successfully inoculated on the gray mouse. There are other members of the favus group that affect the lower animals and occasionally are communicated to man.

Herpes or tinea tonsurans is a form of ringworm attacking the scalp and due to the trichophyton tonsurans, of which there are two principal forms, the **trichophyton microsporon** and the **trichophyton megalosporon.** The small spore parasite, called by Sabouraud the microsporon Audouini, affects children, and its lesions are practically restricted to the scalp; the mycelia penetrate the hairs, which become brittle and readily fragment. Usually there is not much inflammation, although the thread attaches itself to the cuticle of the hair-shaft. The spores vary from 3 μ to 4 μ and extend into the hair a short distance above the bulb. On agar containing one per cent. peptone and three per cent. maltose the organism produces a central elevation, and an areola of powder-like rays, creamy-white in color.

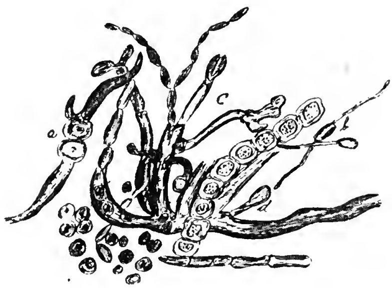


FIG. 89.—FAVUS FROM A MOUSE.—(*Coplin and Bevan.*) ×800 diameters.
a. Germinating tube from gelatin culture. *b.* Conidia. *c.* Formation of fruit. *d.* Mycelial threads with fructification.

Tinea versicolor is due to the **microsporon furfur,** a parasite the hyphæ and mycelia of which are smaller than the parasites described above. The disease affects particularly the trunk and limbs, giving rise to yellow, yellowish, or dark-brown spots or larger areas; the hands, feet, and face usually escape. If small fragments of the desquamating lesion be softened in liquor potassæ, washed in alcohol and ether, and mounted in glycerin, mycelial threads 3 μ to 4 μ in diameter, curved and U-shaped but not ramified, may readily be recognized; round and double contoured spores are also present. Reports of successful cultivation have been made, but remain unverified.

Erythrasma is due to the **Microsporon minutissimum.** The lesion is seen particularly on the inner aspect of the thighs and is manifested by the occurrence of brownish patches with but little desquamation. The parasite can be demonstrated in the desquamated epithelial cells as short mycelia from 0.6 μ to 1 μ in diameter and varying in length from ovoids to threads extending beyond the cell boundaries.

For the demonstration of fungi in dermatomycoses the crusts, epithelial scales, or hairs may be shaken with ether, the excess of which

is poured off and the specimen covered with liquor potassæ; in from a few hours to several days, depending upon the size of the specimen, the tissue softens, dissociates, and can be crushed and examined microscopically. After dissociation in liquor potassæ, staining is usually difficult, although alcoholic solutions of eosin or safranin may be made to tinge the parasites. For staining the hyphomycetes in horny tissues Kraus[1] recommends the methyl-green-pyronin blood stain of Pappenheim, which should be obtained from Grübler. Stain for five minutes, wash and examine in water; sometimes better results are obtained by the method recommended for staining the spirochæta found in syphilis (see page 175).

Thrush, muguet, soor, or preferably **mycotic stomatitis,** is a parasitic affection attacking the various mucous membranes, but especially that of the mouth; it is manifested by redness, more or less catarrhal inflammation, and the development of whitish spots resembling flakes of curdled milk. The causative fungus infiltrates between the epithelial cells, sometimes extending downward into the connective tissue. Mace[2] believes that the infiltration of the epithelium is brought about by change in the action of

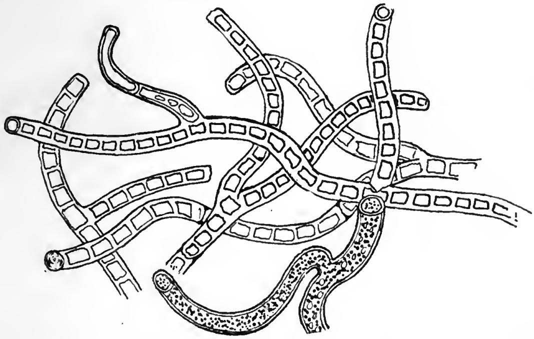


FIG. 90.—MICROSPORON FURFUR.—(*Coplin and Bevan.*) ×600 diameters.

the saliva depending upon antecedent or associated infection by pus cocci, colon bacilli, and possibly other organisms. This explanation, if correct, accounts for the well-known fact that the disease is much more common in the debilitated, and rarely, if ever, attacks a previously healthy individual. The infection may involve the esophagus, and rarely other parts of the alimentary canal. Smith and Radkey[3] report an instance in which the vagina was affected (vaginitis or colpitis mycotica). Dark or brownish thrush areas may result from extravasated blood infiltrating the diseased tissue. Oliver[4] reports a series of cases of mouth infection with a fungus resembling the oidium; some of the patients were otherwise in good health, and most of the cases were chronic. Frisch has found the bladder involved. Hübner[5] records a general infection by the thrush fungus and states that Concetti

[1] "Centralbl. f. Bakt.," Sept. 23, 1904, p. 153.
[2] "L'Obstretique," 1904, viii, No. 6.
[3] "Medical News," June 27, 1903, p. 1204.
[4] "California State Jour. of Medicine," August, 1904, p. 240.
[5] "Deut. med. Woch.," 1903, p. 281.

has shown conclusively that the organism produces an energetic toxin. Zenker and Ritter have reported brain abscesses due to the parasite, and Schmorl has found it in abscess of the kidney and spleen.

The parasite causing thrush has been variously classified by different writers; the names given the germ—oidium albicans, monilia conidia, saccharomyces albicans, thrush fungus, soorpilz, and muguet—indicate the varied views that have been held as to its botanical position; **oidium lactis** is generally preferred. By some authorities the parasite is believed to be intermediate between the moulds and yeasts. It forms branched mycelia and spheric or oval conidia. The branched hyphæ consist of short cylindric cells, which vary slightly in thickness. On milk, bread-paste, potato, and other culture-media the oidium albicans rapidly forms a milk-white growth, extending as thready, almost colorless projections into the substratum. It stains with the usual anilin dyes and by Gram's method.

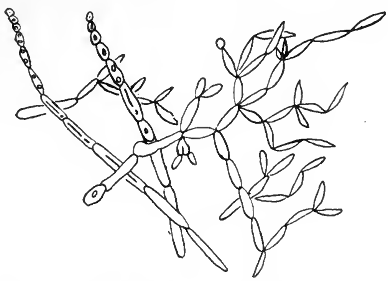


FIG. 91.—OIDIUM ALBICANS (THRUSH FUNGUS).—(*Coplin and Bevan.*)

FIG. 92.—ACTINOMYCES (RAY FUNGUS). FROM BOVINE ACTINOMYCOSIS.—(*Coplin and Bevan.*) × 800 diameters.

Actinomycosis[1] is a disease affecting man and a number of the lower animals, and may be due to any one of several closely allied fungi upon the classification of which authorities are not agreed. The prevailing

[1] See works referred to in foot-note, p. 81. Feistmantel, "Centralbl. f. Bact.," xxxi, 1902, p. 433. Lignieres and Spitz, "Arch. Parasitologie," vol. vii, 1903. Foulerton, "Path. Soc. of London," Nov. 4, 1902. Levy, "Sixth Annual Report of the Michigan Acad. of Sci.," pp. 169–172. McDonald, "Edinburgh Med.-Chir. Soc.," Feb. 3, 1904. Biagi, "Sperimentale," lviii, 4, 1904. Neukirch, "Zeitsch. f. Hyg. u. Infectionskr.," xlviii, 3, 1904. Lagrange, "Gaz. hebd. des scienc. med. de Bordeaux," Nov. 6, 1904. Knox, "Lancet," Oct. 29, 1904, p. 1204. Bodin, "Bull. de la Soc. scient. et med. de l'Ouest," xii, 1903. Enriquez and Sicard, "Soc. Méd. des Hôp.," Paris, May 13, 1904. Burnham, "Johns Hopkins Hospital Bull.," April, 1904, p. 136. Wright, "Amer. Jour. of the Med. Sci.," July, 1904. Poncet, "Acad. de Med.," April, 1904. Meier, "Diss. med. München," 1904. Thevenot, "Gaz. des Hôp.," Nov. 27, 1904. Graff, "Zeit. f. Heilkunde," 1904, Heft 10. Heinrichs, "Arch. f. Laryng. u. Rhinol.," 1904, Bd. 16, p. 350. Löwe, "Diss. med. Greifswald," 1904. Sanfelice, "Centralbl. f. Bakt.," June 16, 1904, p. 355. Dõpke, "Münch. med. Woch.," Dec. 22, 1903. Gilbert, "Zeit. f. Hyg.," Sept., 1904, p. 383. Langer, "Zeit. f. Hyg. u. Infectk.," 1904, Bd. 47, H. 3. Di Donna, "Ann. Ig. sperim.," t. xiv, f. 3, 1904, pp. 449–459. Warthin and Olney, "Amer. Jour. of Med. Sci.," 1904, vol. cxviii, p. 637. MacCallum, "Centralbl. f. Bakt.," Bd. xxxi, No. 12, May 14, 1902. Stokes, "Amer. Jour. of Med. Sci.," Nov., 1903, p. 861. Howard, "Jour. Med. Research," May, 1903, and Jan., 1904.

custom is to regard the parasite of actinomycosis as a streptothrix; the terms nocardia and cladothrix are also used. MacCallum argues strongly in favor of the generic name actinomyces, and, as I strongly concur in his views, I shall adhere to the nomenclature followed in the preceding edition of this book. Studies of the last few years appear to have established that there are a number of closely allied organisms belonging to this group and that the clinical phenomena ordinarily called actinomycosis may be due to any one of several closely related parasites; Stokes gives a table recording a number of the differences between individual members of the group. All of the actinomyces are branching fungi, non-motile, spore-forming, Gram-positive, and give rise to dense, adherent, often shaggy colonies that at first are white or light yellow in color, but in older growths may be dark, almost brown. The actinomyces bovis liquefies gelatin; none of the organisms produce fermentation; members of the group occurring in man are acid-fast, showing a stain reaction similar to that of the tubercle bacillus. The actinomyces in culture are both anaerobic and aerobic, although some forms can not be grown in the absence of oxygen; attempts to make this property a basis of classification have been unproductive. The germ is extremely pleomorphous, giving rise to structures so dissimilar that it often seems difficult to believe that the culture is not contaminated by bacteria. Of the various forms assumed by the parasite the following merit special consideration: The branching filaments rarely exceed 0.5 μ in diameter and in young cultures are uniform; in older growths they may break up into rods or coccoid bodies; the filaments, bacillus-like and coccoid bodies, usually possess a demonstrable outer layer or sheath. In cultures the mycelia extending upward develop spores or gonidia. Toward the periphery of the masses (actinomyces granules) in the tissues, pyriform, club-like bodies possessing great diagnostic significance are usually found. Such bodies develop particularly in the yellowish granules frequently present in actinomycotic tissues and in the pus; club-containing masses resemble grains of iodoform, or—as a result of calcareous deposit—grains of sand.

FIG. 93.—ACTINOMYCES, FROM CULTURE.
The specimen shows branching threads and a few slightly clubbed filaments.

Demonstration.—It is well to remember that in demonstrated actinomycotic lesions the fungus is often absent or can not be detected during long periods. It is most readily found in the discharges from freshly opened lesions, and becomes more difficult to recognize in the presence of active concurrent infection, particularly when the latter is due to other pyogenic organisms. In order to demonstrate the fungus in suspected material (usually pus), spread the matter on a sterile glass plate and search carefully for yellow or yellowish-white grains that closely

resemble granules of iodoform. The largest of these grains will appear about the size of a pinhead. With a needle pick out one of the grains, transfer it to a microscope slide, and gently cover; examined with a $\frac{1}{3}$-inch or $\frac{1}{4}$-inch objective, these grains appear spheroid or globular, greenish in color, and quite opaque. While still in focus, with a needle make pressure on the cover-glass, focusing slowly downward; when the granule falls to pieces, as it soon will, under a higher power ($\frac{1}{6}$-inch dry lens or $\frac{1}{12}$-inch oil immersion), the club-shaped masses become clearly defined. Staining is not necessary, but in sections or cover-glass spreads beautiful results may be obtained by the following: (1) Carbolfuchsin, ten minutes, gently warming the solution; (2) rinse in water; (3) saturated alcoholic solution of picric acid, five to ten minutes; (4) water, five to ten minutes; (5) fifty per cent. alcohol, fifteen minutes; (6) dehydrate in absolute alcohol; (7) clear in clove oil; (8) mount in balsam (Crookshank-Plaut). Sections may also be stained in carbolfuchsin, largely decolorized in fifty per cent. alcohol, washed in water, and followed by hematoxylin in the usual manner. From cultures, the fungus stains with most of the anilin dyes and by Gram's method.

Pure cultures are obtained by plating; the grains, after washing in sterile water, are crushed in the nutrient gelatin, and this is spread as usual. In order to break up the grains and to diffuse them in such a way as to secure pure cultures, it is recommended that they be rubbed up with sterile sand and plated in the usual manner. In from four to seven days the colonies appear, and are then inoculated on agar or gelatin.

The **path of infection in actinomycosis** may be through almost any surface or cavity communicating with the exterior. The frequency with which the disease affects the head and neck speaks strongly for oral infection, probably through some abrasion of the mucous membrane or possibly a diseased tooth. According to Wright, there are six cases of established tonsillar infection. This observer found that in 117 cases of actinomycosis the jaws, mouth, or pharynx were involved in 72. Chiari first described a case of primary infection, probably by mural implantation, of the intestinal wall. Burnham has been able to collect 32 cases of primary actinomycotic appendicitis.

Morbid Anatomy.—Once the fungus secures admission to the connective tissues, there is engendered a granulation tumor containing large masses of lymphoid cells, a few epithelioid elements, and giant-cells, very closely resembling a tubercle; the lessened tendency to necrosis or caseation, however, permits these masses to accumulate and to become of considerable size, when, prior to the discovery of the cause, they were not uncommonly mistaken for sarcomata. The size of the actinomycotic masses varies. The larger nodules, which may attain the dimensions of a fetal head, are not uncommonly honeycombed, resembling a trabecular structure, the stroma of which is formed from the connective tissue of the affected part. The irregular alveoli, produced by the connective tissue, are distended by inflammatory products containing the parasite. When occurring in bone or on the skin, the resemblance to sarcoma may be striking. The contents of actinomycotic masses may, as a result of the pyogenic powers of the germ, be composed of pus. At other times the necrosing and pus-producing properties of the parasite are absent, and in some of these cases a hyaline fibrous

tissue is produced, rendering the affected structure denser than normal (*wooden tongue*); this type corresponds to the chronic productive or hyperplastic form of tuberculosis mentioned on page 153. Like tuberculosis, actinomycotic areas may calcify or encapsulate, or both these changes may be present. Ulcers formed on the skin are crater-like, and discharge a clear, mucilaginous fluid, sometimes in large quantities. The local extension of the process is peculiar, in that it advances steadily, involving contiguous tissues, and does not appear to follow the path of least resistance, such as the course of a muscle, blood-vessel, or nerve, or the lymph-stream. Penetration of venous walls permits the formation of actinomycotic thrombi, which, becoming fragmented, give rise to emboli containing the specific organism. In Ponfick's case such a thrombus occurred in the jugular vein, and later embolic metastasis showed itself in the heart, lungs, spleen, and brain. Probably on account of the large size of the germ, dissemination by the lymph-stream is less common than by the blood-supply.

In over fifty per cent. of the cases in man the lesion is located in the tissues of the head and neck. The intra-abdominal organs are next in point of frequency, the lungs, tongue, and skin following in the order given. Actinomycosis has been observed in the generative organs, particularly in the Fallopian tube; the reported cases of actinomycosis of the female reproductive organs are of special interest, particularly when we take into consideration the fact that only about one-third of all the cases of actinomycosis occur in women. Actinomycosis is also seen in the medulla of long bones and in the cancellous tissue of small bones, and has been described in the mastoid cells and middle ear. Primary pulmonary actinomycosis is not a rare form of the affection; primary cerebral actinomycosis occurs, although brain involvement is usually due to metastasis, the fungus reaching the brain from a primary lesion elsewhere. The frequency and mortality in different forms of actinomycosis are shown by the following statistics by Poncet and Thévenot.[1] Of the 306 cervico-facial cases, 10 are dead, 3 improved, 168 cured, while in 125 the result is not known. Among 25 infections of the thoracic or abdominal wall, 4 are dead, 16 cured, and in 5 the result is unknown. The viscera of the abdomen were involved in 84 cases, 16 of which are believed to have been cured, 17 are dead, and 51 could not be traced. Of 71 pleuro-pulmonary cases, 4 are cured, 25 dead and in 42 the subsequent history could not be obtained.

Mycetoma, also called Madura foot or fungus foot of India, is due to a parasite possessing the general characters of other members of the actinomyces group, called the **Streptothrix maduræ.** Two forms of the disease have been recognized, one in which the discharged granules are black (gunpowder grains) and the other in which they are white or yellow (ochroid). Laveran[2] believes that the two varieties are distinct, and that both differ from the ordinary actinomyces of man and cattle; he would make the streptothrix mycetoma a distinct parasite.

Demonstration.—The parasite may be identified in the tissues or discharges by a method similar to that recommended for actinomyces. The ochroid and melanoid granules may be crushed and examined under

[1] "Méd. Mod.," June 10, 1903, p. 181.
[2] "Bull. de l'Acad. de Méd.," 1903, vol. xlvii, p. 773.

the microscope, when mycelial threads will usually be recognized. There is a similar ray-like growth with slight enlargement at the ends of the filaments, but not the typical clubs of actinomyces.

Usually but one foot is affected. Both macroscopically and microscopically the lesion resembles actinomycosis, and is essentially chronic, often persisting for years. It is a slowly spreading inflammatory process, characterized by the formation of granulation tissue in which necrotic, degenerative, and suppurative processes occur; the overlying skin breaks, giving rise to sinuses from which a serous or serosanguineous discharge escapes. It commonly begins in the sole of the foot or in a toe, and rarely extends beyond the ankle; the bones soften and necrose, and even such dense structures as tendon and ligament yield before the advancing granulation tissue. The parasite shows practically no tendency toward generalization.

Streptothricosis is commonly used to cover all lesions produced by fungi resembling the streptothrix, usually including infections by the actinomyces. The most important type of streptothrix infection not already considered is that involving the lung—**pulmonary streptothricosis.** Warthin and Olney[1] have recently reported a case and collated others from literature. The acid-fast branched threads are abundant in the sputum, which may also yield cultures. Similar streptothrix elements may be found in the sputum, coming from large tubercular cavities, dilated bronchi, or gangrenous areas in the lungs; in many of these cases the infection is clearly secondary; it may intensify previous lesions or give rise to independent extension.

Leptothricosis[2] is an infectious process due to invasion of the tissues by members of the leptothrix group. The botanical position of these germs is even less accurately determined than that of the actinomyces, from which they differ in that true branching is not present. In one of Pearce's cases the parasite was the only organism present in gall-stones. **Mycosis tonsillaris benigna** and **Pharyngomycosis leptothrica** are names applied to a chronic infection involving the tonsils, pharynx, or base of the tongue; rarely the larynx and esophagus are affected. In this condition the whitish patches on the surface, or the plugs extending into the tonsil, are composed largely of leptothrix mycelia. The organism may readily be detected by the usual anilin dyes, but is not easily cultivated.

SACCHAROMYCETES.[3]

Blastomycosis or **Saccharomycosis,** preferably the former, is applied to diseases produced by yeasts. These bodies, well known in the arts, consist of oval, round, or nearly spheroidal cells of varying sizes, commonly slightly larger than a red blood-cell. Proliferation by budding is the usual method of reproduction, and if the *Saccharomyces cerevisiæ*—ordinary domestic yeast—be watched under the microscope,

[1] "Amer. Jour. of Med. Sci.," vol. cxxviii, p. 637.

[2] Leptothrix infection in man and animals has been considered in detail by Pearce, "Univ. of Penna. Med. Bull.," Aug., 1901, and November, 1902; full bibliography.

[3] "Centralbl. f. Bakt.," Aug. 19, 1904, p. 529. An elaborate systematic classification of the Saccharomycetes. Guilliermond, "Bull. de l'Inst. Pasteur," March 15, 1905, p. 178.

the formation of buds which enlarge and give rise to new cells can readily be recognized. Often the new cell adheres to the parent, and by continuation of this process short chains and irregular groups are formed. Most yeasts may be cultivated on all the laboratory media, and grow especially well on nutrients containing sugar, which they ferment with the production of alcohol. Büchner has shown that the activity of yeasts depends upon a ferment contained in the interior of the cell; this substance he has expressed from the plant and utilized for the production of fermentation.

With regard to the pathogenic action of yeasts in man our information is incomplete; they are sometimes found in the stomach, occasionally in the stools, and Bendeler[1] has shown that they may occur in the urine. Recently Klein and Gordon[2] have reported an epidemic affection of the throat resembling diphtheria, tonsillitis, and scarlet fever, but apparently due to a yeast, which they call the *Saccharomyces hominis*. Yeasts have been found in tumors, and certain observers believe them to be a cause of neoplasm.[3] The Saccharomyces neoformans has not been generally received with enthusiasm, and the observations of Sanfelice still lack confirmation. Cleary[4] reports a case of generalized blastomycosis, and collates four others from literature. When the parasite enters the circulation, pulmonary localization is an almost constant phenomenon.

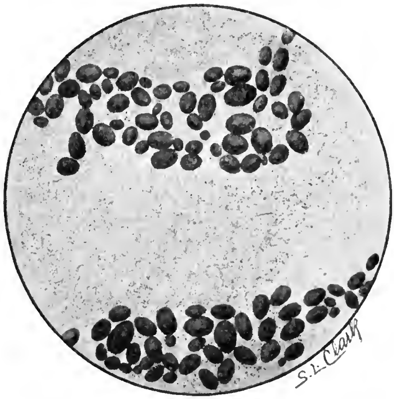


Fig. 94.—Yeast Cells from Pure Culture. Budding Forms are Present.

The name **blastomycetic dermatitis**[4] is applied to a form of cutaneous blastomycosis due to a pleomorphous organism resembling and usually classed with the yeasts. In the tissues and discharges the parasite is found as a spherical cell 10 μ to 15 μ in diameter, double contoured, often budding, and sometimes containing intracellular structures that may be spores; it grows best on beerwort, glycerin and glucose agars, which should be slightly acid. Successful cultures develop in from two to sixteen days, and, according to Ricketts, on agar, or beerwort agar slants, may be (1) a smooth, whitish, pasty growth without aërial hyphæ, and may or may not penetrate the medium. In

[1] "Centralbl. f. Bakt.," Jan., 1905, p. 55.

[2] Thirty-second Annual Report of the Local Government Board, 1904, p. 559.

[3] Sanfelice has been a most ardent advocate of this view; his extensive observations and writings on the subject may be traced from his papers in the "Rif. Med.," Sept. 9, 1902, and "Zeit. f. Hyg. Infectkrank.," 1903, Bd. xliv, p. 64.

[4] "Trans. Chicago Path. Soc.," May, 1904, p. 105.

[5] Montgomery, "Jour. Amer. Med. Assoc.," June 7, 1902. Wilder, "Jour. Amer. Med. Assoc.," Dec. 31, 1904. Sequeira, "Brit. Jour. of Dermat.," April, 1903, p. 121. Koehler and Hall, "Jour. of Cutaneous Diseases," Dec., 1904. Gilchrist, "Johns Hopkins Hosp. Bull.," Feb., 1904.

this form budding is usually conspicuous, although mycelial growth is often present. (2) The surface is granular or plicated; sometimes spicules extend upward, but aërial hyphæ are absent. (3) Growths resembling either of the first groups, but conidia with aërial hyphæ are also present.[1] Gilchrist believes that the second and third forms are identical.

Morbid Anatomy.—The disease is a chronic inflammatory process, primarily local, developing as a papule which becomes a pustule covered by crusts. It extends laterally by the formation of minute dermal and subdermal abscesses which usually are of microscopic dimensions. Extensive hyperplasia is present in the rete, the cells of which can project into the corium. Mast-cells and giant-cells are frequently present, the latter often containing parasites. The organisms can be recognized in sections stained with hematoxylin and eosin, but better results are obtained with methylene-blue. The fungus may be demonstrated by placing fresh, hardened, or teased particles of tissue, or pus, on a slide, dropping on a ten to thirty per cent. solution of potassium hydrate or equal parts of liquor potassæ and glycerin, and applying a cover-glass. In such preparations the organisms appear as double-contoured, highly refractile bodies, in some of which granular contents, vacuoles, or shining spore-like bodies can be demonstrated (Montgomery).

SPIROCHÆTA.

The **spirilloses** include a number of diseases occurring in man in which spiral organisms of an imperfectly determined nature are found. Usually these parasites have been grouped with the bacteria, but the recent studies of Schaudinn[2] strongly controvert this view and place them with the animal parasites, making them closely related to the trypanosomes. Parasites of this type have been found in the owl and the goose. In man the diseases in which spiral organisms of this kind have been found are relapsing fever, Vincent's angina, and, more recently, syphilis. From none of these has the organism been obtained in pure culture.

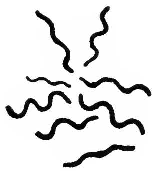


FIG 95.—SPIROCHÆTA OBERMEIERI (SPIRILLUM OF RELAPSING FEVER).—(*Coplin and Bevan.*) × 800 diameters.

Relapsing fever[3] is due to an actively motile, delicate, flexible spiral organism, 16 μ to 40 μ in length and of scarcely measurable thickness. The number of complete spirals in one organism may be from ten to fifteen. According to Sandwith, the motion is chiefly lateral and rotary. The parasite may be so active that it is with difficulty kept in the field of the microscope.

Demonstration.—During the crisis the organisms are present in the blood in large numbers. They are less abundant just before the occurrence of the crisis, and after it is past they disappear rapidly. They are not present in the peripheral circulation during the nonfebrile period. In

[1] Ricketts, "Trans. Chicago Path. Soc.," May 9, 1904, p. 113.

[2] "Generations und Wirtswechsel bei Trypanosoma und Spirochæte," Arbeit. a. d. kais. Gesundheitsamte, Bd. xx, H. 3, 1904, pp. 387–439.

[3] Quite full references to the older articles will be found in Allbutt's "System of Medicine," vol. i, p. 958. See also recent paper by Sandwith, "Practitioner," May, 1904, p. 653.

order to demonstrate the presence of the organism in the blood, the finger or lobe of the ear is properly cleansed, disinfected, and pricked by a needle. (See Part III, chapter on Diseases of the Blood.) A drop of blood is received on a slightly warmed slide and a cover-glass is at once applied. As soon as the blood flows near the margin of the cover-glass a ring of oil or vaselin should be painted around the cover-glass in order to prevent too rapid drying during the progress of the examination. As the organism possessed a transverse diameter approximately that of the cholera spirillum, it will be necessary to conduct the examination with high powers. The presence of spirilla is indicated by the agitation of the corpuscular elements. At first the spirals may be too active to be readily focused upon, but in a short time they become sufficiently quiet to permit examination. Just before and during the crisis the number of spirilla may approach one organism for every twenty erythrocytes. After the disappearance from the peripheral circulation Metchnikoff has succeeded in demonstrating them in the splenic pulp. In moist films or in suspension in normal salt solution the motility may be evident for twelve hours or longer. The organism is evidently destroyed by a comparatively low temperature, a fact which has been taken to indicate the absence of spores, but also supporting the belief that it belongs with the animal parasites. Dry films, prepared as described in the chapter on The Blood, may be stained as directed for other bacteria. It is probable that the spirillum of relapsing fever will stain by the same methods as the organism found in syphilis, and also by Wright's method. It can also be tinged by aqueous solutions of gentian-violet, Bismarck brown, or fuchsin.

FIG. 96.—SPIRILLUM OF VINCENT AND THE FUSIFORM BACILLUS; OTHER ORGANISMS ARE ALSO PRESENT.—(*From case reported by Dr. Rosenberger.*)

Pathogenesis.—The parasite is always demonstrable in some stage of relapsing fever; with the advancing pyrexia the organisms increase, and disappear during defervescence. The disease may be transmitted to man and monkeys by inoculation with the infected blood. When death has resulted from relapsing fever, the skin commonly shows a characteristic yellowish hue. Various changes—fatty and granular—have been described in the heart; the spleen is enlarged and softened, the follicles swollen, and the pulp darker than normal. The liver may be enlarged, the cells fatty and granular, and in some cases round-cell infiltration in the neighborhood of the portal vein occurs. Granular and fatty changes, sometimes with hemorrhages, are found in the kidney. In some cases the interstitial tissue is infiltrated, but the change is not characteristic.

Ulcero-membranous stomatitis or angina, also called **diphtheroid**

angina and **angina of Vincent**,[1] is a disease affecting particularly the tonsils, gums and uvula, less commonly the oral and pharyngeal mucosa or lips; it is characterized by the formation of a superficial membrane, and, in marked cases, necrosis extending into the submucosa. In severe infection parts of the uvula may be destroyed. The membrane is yellow, or greenish-yellow, and when detached leaves a bleeding or eroded surface; glandular enlargement is variable. The actively motile spirochæte varies in length from 10 μ to 30 μ, and, like the organism found in relapsing fever, is extremely tenuous and never stains with the same intensity as the symbiotic bacillus. The spirillum is usually associated with a fusiform rod-shaped organism (Bacillus fusiformis) 5 μ to 10 μ in length and 0.6 μ at its widest point; both organisms are Gram-negative. Wright believes that the fusiform organism is not a bacillus, and calls attention to the fact that the incessant whip-like movements of the spirillum vividly recall the actively moving flagellate bodies seen in malarial blood; he suggests that both organisms may be modifications or stages in the evolution of the same parasite.

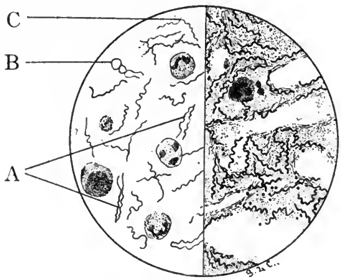


FIG. 97.—SPIROCHÆTA PALLIDA.

Left half, Giemsa stain, spread from congenital syphilis.
Right half, Levaditi stain of section of lung, congenital syphilis; this (silver method) makes the organisms appear much broader.
A. Pairs united at one end.
B. Twisted pairs.
C. Double length, apparently dividing form.

Syphilis[2] is a chronic infectious disease the exact cause of which has long eluded accurate determination. Lustgarten described a bacillus to which he attributed the disease. Other bacteria alleged to be etiologic agents in syphilis have been brought forward by de Lisle and Jullian, Joseph and Piorkowski, and others; Schuller describes an animal parasite which he believes to be the cause. The relation of these organisms to syphilis was never established, and at present the **Spirochæta**

[1] See works referred to in foot-note, p. 81; also Rosenberger, "Amer. Med.," July 23, 1904, p. 161; Bruce, "Lancet," July 16, 1904, p. 135; Wright, "Lancet," July 9, 1904; Veszprémi, "Centralbl. f. Bakt.," Bd. xxxviii, 1905, p. 136, "Cultivation and Animal Experiments on the Bacillus fusiformis and Associated Spirillum."

[2] References to bacteriology of syphilis can be obtained from the current works named in the foot-note on p. 81. "Successful Inoculation of Syphilis on Apes," see Metchnikoff and Roux, Third Memoir, "Annales de l'Inst. Pasteur," Nov. 25, 1904, p. 657, where reference to their own and other previous studies may be found; also Lassar, "Dermatolog. Zeit.," xi, No. 8; Neisser, "Deut. med. Woch.," 1904, p. 1369; Zabolotny, "Arch. sci. Biol.," vol. xi, Nos. 1 and 2, p. 155; full discussion before Tenth Congress of Dermatology, Berlin, Sept., 1904; Salmon, "C. R. Soc. de Biol.," June 11, 1904; Arnal and Salmon, "Annales de l'Inst. Pasteur," July 25, 1904; Tomasczewski, "Deut. med. Woch.," 1903, No. 26; Hoffmann, "Berl. klin. Woch.," Feb. 6, 1905, and Queyrat, "Soc. méd. des Hôp.," Jan. 13, 1905. Piorkowski, "Berl. klin. Woch.," Sept. 19, 1904, "Successful Inoculation of a Horse." Klingmüller and Baermann, "Deut. med. Woch.," 1904, "Non-filterability of Syphilitic Virus." For recent study of immunity in syphilis see Nagelschmidt, "Ueber Immunität bei Syphilis nebst Bemerkungen über Diagnostik und Serotherapie der Syphilis," Berlin, 1904. Literature of the recent work on the spirochæta of syphilis is given in full by Flexner and Noguchi, "Med. News," June 17, 1905, p. 1145; also McWeeney, "Brit. Med. Jour.," June 10, 1905, p. 1262.

pallida—also called **Treponema pallidum**—discovered by Schaudinn and Hoffmann is accepted as the cause. This organism has been identified in syphilitic lesions, both natural and experimental, and has not been found in any other infection. The organism may also be found in the fluids aspirated from enlarged glands and in the curetings and expressed juices of the initial lesion. It is $4\ \mu$ to $14\ \mu$ in length and does not exceed $0.5\ \mu$ in diameter; it is actively motile, rotating on its axis, bending, shortening, and lengthening the spirals. In some organisms a suggestion of an undulating membrane has been observed; flagella have not been demonstrated. In the superficial lesions of syphilis the parasite is associated with a larger and more readily stained spirochæta (Spirochæta refringens); the latter has not been found in the deeper syphilitic lesions.

Demonstration.—The organism is difficult to stain; indifferent results are obtained by the use of anilin-oil-gentian-violet solution, and most of the ordinary bacterial stains are unsatisfactory. For its demonstration the discoverers recommend the following: Giemsa's eosin solution (2.5 c.c. of a one per cent. solution of eosin, in 500 c.c. of water), 12 parts; azure I (1 to 1000 aqueous solution), 3 parts; azure II (0.8 to 1000 aqueous solution), 3 parts; the prepared stain does not keep. Air-dried, thinly spread films are fixed in absolute alcohol for ten minutes and left in the stain twenty-four hours, washed in water, dried in the air, and examined in cedar oil. Wright's or Leishman's blood stains may be used.

Syphilis may be inherited or acquired. **Hereditary syphilis** may result from parental infection of the ovum or spermatozoon, or the mother may infect the fetus by syphilis acquired after impregnation. Syphilis transmitted to the child during delivery is an acquired form of the disease.

Syphilitic poison exerts a deleterious influence on the developing infant, which as a result not uncommonly dies; fibroid and thrombotic processes occur in the placenta or maternal sinuses and interfere with proper nutrition of the child. A large percentage of syphilitic women abort; when, however, the offspring survives, it is usually ill-nourished, wasted, and may be born with some of the external manifestations of syphilis, or these may develop later. At birth there may be numerous blebs on the skin with areas in which the surface is excoriated, resembling the cutaneous maceration seen in still-born infants. A catarrhal rhinitis (snuffles) and other disturbances of the mucous membranes may be present. The pathognomonic eruption of hereditary syphilis is a pemphigus, which may be present at birth; in the affected areas the epidermis is elevated, giving rise to characteristic blebs containing a sanguinolent or greenish fluid. Pustular eruptions resembling the skin lesions of variola sometimes occur. The vesicular pemphigus is most frequent on the palms and soles, and the pustular form on the buttocks and around the genitalia; erythematous rashes are common. Paronychia, dactylitis, and interstitial keratitis further illustrate the protean nature of the affection. A characteristic form of osteochondritis develops in the epiphyseal junction of the long bones. On section, these structures, particularly the lower end of the femur, the apophyso-epiphyseal junction, is broadened, yellowish in color, and may contain areas of pus-like softening; this condition is called **syphilitic osteochondritis.** Microscopically the zone of developing bone is broadened

irregular, contains an excess of embryonal and giant cells, and while at first the calcific deposit is excessive, later calcification ceases and the previously deposited lime salts may be absorbed. The epiphyses may be enlarged and occasionally they separate from the shafts (epiphyseolysis). Marfan found that in one-half of the cases of congenital syphilis the spleen is increased in size, and that splenic enlargement in infants is most commonly due to syphilis. The liver in hereditary syphilis is usually larger than normal as a result of diffuse interstitial hepatitis with or without gummata. Stoerk[1] reports an instance of renal hypoplasia attributed to congenital syphilis. Massalongo[2] and Guthrie[3] have reported chronic interstitial nephritis due to congenital syphilis. Coupland[4] and Stroeb[5] record instances of acute interstitial nephritis in congenital syphilis; Speiss[6] found renal disease in ten of thirty-four syphilitic children. Barlow,[7] Chiari,[8] and others have reported true arteritis occurring in congenital syphilis and leading to various visceral alterations due to interference with blood-supply. The teeth erupt irregularly, develop unevenly, are structurally altered, and frequently decay early. One of the most characteristic lesions of hereditary syphilis is seen in the upper permanent median incisors. These are peg-like, short, and the cutting-edge marked by a crescentic excavation. According to Paton,[9] hereditary syphilis may cause the following joint manifestations: (1) simple synovial effusion; (2) joint disease associated with syphilitic epiphysitis; (3) primary gummatous infiltration of the synovial membrane; (4) osteitis associated with effusion only; (5) osteitis with gummatous disease of the synovial membrane; this variety has been termed pseudo-white-swelling; (6) deforming arthritis or the deforming arthropathy of Fournier. Orchitis was present in 5 of Still's[10] 64 cases. Oligocythemia and oligochromemia are commonly marked. Mucous patches are almost always present and deep refractory fissures at the angle of the mouth may, on healing, leave radiating scars.

Fournier's[11] recent statistics show what a disastrous influence syphilitic poison exerts on gestation and on the infant. In 366 pregnancies there were 115 abortions, and 174 of the infants born alive died during the first years of life; 31 (8.5 per cent.) of the remainder were in good health. In 45, mental and physical development was retarded; 43 showed lesions of the skeleton; in 42 there was ocular disease. The nervous system was affected in 39. He also records 19 observations clearly establishing that inherited syphilis may be transmitted to the offspring. Of the 333 pregnancies recorded by Neumann,[12] 156 terminated in abortion; 24 children were still-born, 43 were syphilitic, and 79 showed no evidence of the disease.

[1] "Wien. klin. Woch.," 1901, No. 41.
[2] International Congress, Rome, 1894.
[3] Report of the Society for the Study of Diseases in Children, 1901, p. 69.
[4] "Trans. Path. Soc. of London," 1876, vol. 27, p. 303.
[5] "Centralbl. f. allg. Path.," 1891, vol. ii, p. 1009.
[6] Inaug. Diss., Berlin, 1877.
[7] "Trans. Path. Soc. of London," vol.28, p. 287.
[8] "Wien. klin. Woch.," 1898.
[9] "Brit. Med. Jour.," Nov. 28, 1903, p. 1389.
[10] "Lancet," Nov. 19, 1904.
[11] "Société Francaise de Dermatologie et de Syphiligraphie," July 6, 1904.
[12] "Wien. klin. Woch.," No. 20, 1904, p. 262.

Although **acquired syphilis** is essentially a venereal disease, Buckley[1] has been able to collect over 9000 cases of extragenital infection. In 4634 cases of syphilis Neumann[2] found 207 instances of extragenital, and 157 of perigenital chancre; of the former, 106 were on the lips and 27 on the hands.

Syphilitic manifestations may be grouped in seven stages: (1) local incubation, (2) period of initial lesion, (3) secondary or systemic incubation, (4) period of secondary symptoms, (5) intermediate period, (6) tertiary period, (7) period of parasyphilitic manifestations. These arbitrary divisions commonly made by systematic writers are convenient for descriptive purposes, but often the disease is disinclined to follow them. The period of incubation varies from ten days to six weeks, averaging about three weeks. The secondary symptoms come on in about six weeks to two months after the beginning of the chancre, and last from two weeks to three years. The intermediate period is of indefinite duration and often absent. The tertiary and parasyphilitic manifestations are essentially late and permit of no trustworthy statement as to their duration. The lesions occurring in the parasyphilitic stage of syphilis are differentiated from all the earlier manifestations by the fact that they are uninfluenced by the usual antisyphilitic remedies.

Morbid Anatomy.—The initial lesion of syphilis—the **chancre**—occurs at the point of inoculation, and is usually solitary, although Pierron[3] records an instance of six separate chancres on the penis. Queyrat[4] reported a case in which 11 chancres developed in succession. Metchnikoff inoculated an ape on October 26 and again on November 5, 1904; a chancre at the point of first inoculation appeared in twenty-six days, and a second chancre followed twenty days after the second inoculation. These and similar observations go to show that insusceptibility to further infection is not coincident with the appearance of the initial lesion.

Histologically the chancre[5] consists essentially of a new growth in the skin or mucous surface, followed by hyaline degenerative and necrotic processes, which usually terminate in ulceration. The first changes occur at the point of infection, and consist of slight edema which becomes more marked and contains demonstrable fibrin; this serous exudate extends into the underlying connective tissue and is promptly followed by a cellular infiltration composed of plasma and typical lymphoid cells, and round cells containing vesicular nuclei; in the absence of mixed pyogenic infection polymorphonuclear leukocytes are not present. The cellular accumulation is most conspicuous around the capillaries and small veins, in both of which thrombi form; the vascular endothelium proliferates. Over the center of the chancre the epidermal strata are thinned, while at its margin the epithelium proliferates. The mass is now an indurated node the firmness of which constitutes one of its most characteristic features, hence the name "hard chancre." The

[1] "Syphilis of the Innocent," p. 30.
[2] "Wien. klin. Woch.," Sept. 25, 1902, p. 1001.
[3] "Arch. de Med. et de Pharm. Mil.," No. 2, 1903.
[4] "Lancet," Sept. 10, 1904, p. 779.
[5] Recent literature on histology of chancre, see Arnal and Salmon, "Ann. de l'Inst. Pasteur," July 25, 1904, p. 465; Ehrman, "Arch. d. Dermat. u. Syph.," 1904, lxviii, No. 1; Bose, "C. R. Soc. de Biol.," 1904, vol. 57, p. 104.

extreme hardness of the mass is often useful to differentiate the lesion from ulcerative or inflammatory processes arising from other causes. When the process is associated with a mixed infection, inducing more or less rapid liquefaction of the proliferate, induration is sometimes inconspicuous, or may even be absent. The view that absence of induration is, to a certain extent, dependent upon the character of the tissue infected, does not seem to be tenable, as so distinguished an observer as Hutchinson maintains that any tissue may suffer induration, and that chancre in any area is commonly associated with the occurrence of this phenomenon. As the blood-vessels are the seat of endothelial proliferation and thrombosis, the blood-supply is proportionately lessened, leading to liquefaction necrosis of the overlying epithelium; an ulcer does not always form, liquefaction necrosis does not always occur, and occasionally a chancre will be observed in which the epithelial covering remains unbroken. When ulceration does occur, a cup-like or scooped-out ulcer forms, its edges are not undermined, and it is not likely to be sloughing or phagedenic. With the subsidence of cellular infiltration, repair begins; the fluid exudate and cells are removed, fibroblasts are formed, and gradually resolution is accomplished.

Associated with the initial lesion, the nearest anatomic lymph-nodes show the alterations incident to infection. In some instances the local lymphatic involvement usually manifested during the activity of the initial lesion escapes observation, or, possibly it is not present. During this process the lymphoid structures proliferate and become more or less edematous, thereby bringing about induration and considerable enlargement of the lymph-nodes functionally nearest the initial lesion. If pyogenic bacteria gain ingress through the ulcer or by other routes, the glandular swelling and hyperplasia may terminate in suppuration; when suppuration does not ensue, which is usually the case, the infiltration and induration gradually subside.

Following the phenomena just described, a stage of apparent quiescence ensues, which, as in other infective diseases, constitutes the period of systemic incubation. This persists for from ten days to six months; the extremes given are unusual, the secondary phenomena commonly manifesting themselves in about six weeks. The lymph-nodes (it is probable that all the lymphatic structures participate; certainly, all that can be discerned from the surface) show a varying amount of induration and swelling; not, however, manifesting any tendency to suppuration. The affected lymph-nodes are freely movable, show no tendency to become confluent or adherent to adjacent structures, and vary in density from relatively soft masses to extreme induration. Syphilis has now passed into the secondary stage, and multiple cutaneous lesions occur; these are clinically important, but pathologically they are not essentially different from many skin lesions that arise independent of syphilis. Syphilitic eruptions are commonly characterized by their polymorphism and their symmetric distribution. The exanthem is not restricted to the skin, but appears also on the mucous membranes. The cutaneous and mucous lesions of secondary syphilis usually involve the superficial layers of the mucosa and the skin, rarely extending sufficiently deep to justify their being considered ulcerative. During this stage, usually at its beginning, there is commonly malaise and slight fever (*syphilitic fever*). The intensity of the infectious processes may

be further indicated by the occurrence of inflammation of the iris or retina, joint and bone pains, splenic and hepatic enlargements, and alopecia.

A most conspicuous lesion of this stage is the so-called *mucous patch*. This appears on the mucosa of the mouth, on the genital mucous membranes, and upon the anal mucosa; a similar, if not identical, lesion is seen on the skin near the anus. A typical mucous patch rarely attains a maximum diameter of 1 cm. and is sometimes covered by a bluish-white membrane, in which case it is called an *opaline patch*. These patches result from superficial necrosis and exfoliation of the epidermis involving part of the Malpighian layer, with degenerative and proliferative changes in the latter; there is also more or less infiltration of the underlying connective tissue. The round-cell elements present in the base of the ulcer are never so abundant as in the initial sore; the resemblance, however, is striking, and the essentially infectious nature of the lesion is further indicated by the fact that the disease may be as readily communicated by the discharges from such surfaces as from the initial lesion. The spirochæta described by Schaudinn and Hoffmann is present in the primarily enlarged lymph-nodes, the general lymphatic enlargements, and in the mucous patches. Females transmit syphilis more frequently by the last named lesions affecting the vulva and vagina than by the chancre, and syphilis of the innocent is usually the result of contact, immediate or mediate, with the highly infective discharges to which it gives rise. Instruments, soiled linen, dressings, drinking cups, knives, forks, and spoons may be carriers of the poison, which has also been transmitted by the tattooing needle and communion cup and by kissing.

The tertiary lesions, which are pathognomonic, are the **gummata, syphilomata,** or **granulation tumors** of syphilis. Gummata are developed as masses of embryonic cells, containing lymphoid and epithelioid cells, with a very slight amount of trabeculæ; occasionally, giant cells are present; coagulation necrosis, hyaline degeneration, and fatty change may cause the center to resemble caseous material. Rarely a true caseation, indistinguishable from that seen in tuberculosis, occurs. The retrograde changes attacking gummata are necroses rather than degenerations, and are probably due to the syphilitic poison and not to the obliterative processes affecting the native and newly formed vessels in the growth; both the vascular alterations and the necrosis are due to the same cause. Occasionally secondary infection may give rise to suppuration. When superficially situated, necrosis of the overlying tissue—skin or mucous membrane—leads to infection and suppuration. With destruction of the overlying tissue there commonly appears a central necrotic core, which separates slowly. In the absence of treatment the necrosis (ulceration) extends peripherally, and in some instances in depth as well. At the present time necrosis and ulceration are rare in recognized gummata. Granulation tumors of syphilitic origin vary in size from purely microscopic bodies to masses five, ten, or even fifteen centimeters in diameter, the latter commonly resulting from confluence of smaller primary gummatous areas. At first the gumma is hard; later, with beginning degeneration in the newly formed elements—or more frequently as the result of necrosis—it becomes sufficiently soft to resemble a cold abscess or to manifest pseudofluctuation and be mistaken for a cyst.

Gummata are sometimes multiple, occurring simultaneously in a number of the tissues and organs. A single nodule is, however, the rule. Syphilomata may occur in nearly all the tissues, but are most frequently observed in connection with the periosteum, particularly that of the cranial bones. Frequently, they are situated in the subcutaneous tissue; they also occur in the liver, kidney, and lung, and even in the heart. The brain is not infrequently affected. In the mucous membranes—particularly of the larynx, trachea, nose, and pharynx—and in the rectum extensive tissue destruction may result. With ulceration, or even in its absence, the subsequent cicatrization may give rise to narrowing of those tubes the walls of which are involved. Such strictures are seen in the rectum and in the trachea.

Parasyphilitic manifestations follow syphilis, but have little or no morphologic resemblance to the frank changes which it induces. For the term parasyphilis[1] and its derivatives Fournier, the eminent French syphilographer, is responsible. Ogilvie happily defines a parasyphilitic affection as syphilitic in origin but not in nature. There is some want of distinction between the really syphilitic and parasyphilitic affections. The diseases of the nervous system following syphilis (for example, dementia and tabes in acquired syphilis, and mental defect and internal hydrocephalus in the congenital form) develop none of the histologic changes seen in the familiar lesions of syphilis; that they may follow and be due to syphilis, there can be no doubt.

[1] Fournier's monograph is in French. Post, "Boston Med. and Surg. Jour.," Oct. 15, 1903, summarizes this subject; see also Ogilvie, "Lancet," June 13, 1903, p. 1647.

CHAPTER VI.

ANIMAL PARASITES AS CAUSES OF DISEASE.

The animal parasites that occur in man may be considered in three general groups: (I) Protozoa, (II) Vermes, (III) Arthropoda. It is not within the scope of this work to deal with the general zoology of parasites or to consider them exactly in their zoologic order. For special consideration of these facts the reader is referred to standard treatises on the subject.[1]

Amebiasis is a term proposed by Musgrave and Clegg for diseases due to **amebas.**[2] Amebas are protozoa[3] belonging to the rhizopoda. Forms not known to be pathogenic have been found in the mouth, feces, vaginal discharges, and in the urine. The relation of the Amœba gingivalis and the Amœba buccalis to disease processes remains undetermined. The most important members of this group are those found in the intestine, called by Schaudinn entameba, of which he recognizes two forms. (1) The **Entamœba coli** he regards as a normal inhabitant of the upper portion of the colon and present in the stools whenever any diarrheal process hastens evacuation of the intestinal contents. (2) This, the second form, he calls the **Entamœba histolytica,** or, from the disease with which it is quite commonly associated, the Entamœba dysenteriæ. He shows by certain peculiarities in its encystment and reproductive phenomena that it differs materially from non-pathogenic amebas. The Entamœba histolytica is 12 μ to 35 μ or 40 μ in diameter, and while living and fully developed actively motile. The nucleus when demonstrable is round or ovoid, the protoplasm granular and often vacuolated; the phagocytic power of the parasite is shown by the frequency with which its protoplasm contains red blood-cells, leukocytes, bacteria, and granular detritus. Pure cultures of the ameba have not been obtained; they may, however, as shown by Musgrave and Clegg, be grown upon agar in symbiosis with bacteria.

Demonstration.—For the technic of cultivation the reader is referred to the monograph by Musgrave and Clegg. A satisfactory recognition of the parasite, particularly in the hands of the novice, demands that he should see it send out pseudopodia; he should observe active movement. In order to do this, the material should be reasonably fresh. In the case of feces, admixture with urine is to be avoided. A drop of the suspected material is placed upon a

[1] Braun, "Tierschen Parasiten des Menchen," 1908. Also Doflein, "Lehrbuch der Protozoenkunde, Jena, 1909.

[2] See papers by Harris, and by Futcher, "Jour. Amer. Med. Assoc.," Aug. 22, 1902. Craig, "Amer. Med.," Feb. 20, 1904. Schaudinn, "Arb. a. d. Kais. Gesundheitsammte," Bd. xix and xx. Musgrave and Clegg, Bulletin No. 18, Bureau of Government Laboratories, 1904. Calkins, "Arch. f. Protistenk.," 1904, p. 1. Castellani, "Centralbl. f. Bakt.," Jan. 25, 1905, p. 66.

[3] Calkins, "Protozoölogy," 1909. Clarke, "Protozoa and Disease," 1903. Doflein, reference given above.

slide and a cover-glass applied. The slide may be gently warmed, or the microscope may be kept in a reasonably warm place, under which conditions movement will be more active. Fresh specimens may be best stained by mixing with the suspected material, placed upon a slide, a drop of a watery solution of toluidin blue. This reagent acts as a fixative and at the same time stains the amebas intensely and rapidly. Pieces of tissue are best fixed in corrosive sublimate, embedded in paraffin, and the sections stained in eosin, followed by toluidin blue for twenty or thirty minutes; wash and differentiate in alcohol, clear in cedar oil or xylol, mount in balsam.[1] For the demonstration of amebas in tissue or pus Mallory[2] recommends the following method, which does not yield satisfactory results when the parasites are in feces: (1) Fix in alcohol; (2) section by celloidin or paraffin method, preferably the latter; (3) stain sections in a saturated aqueous solution of thionin three to five minutes; (4) wash in water; (5) differentiate in 2 per cent. aqueous solution of oxalic acid one-half to one minute; (6) wash in water; (7) dehydrate (celloidin sections 95 per cent. alcohol, paraffin sections absolute alcohol); (8) clear (celloidin sections in oleum origani cretici or oil of bergamot, paraffin sections go direct to xylol); (9) wash in xylol; (10) balsam. The nuclei of amebas and granules of mast cells are brownish-red, other nuclei are blue.

Pathogenesis.—The morbid anatomy of amebic dysentery and its complications will be considered in Part III of this book, in chapter dealing with Diseases of the Alimentary Canal; amebic abscess is described with abscesses of the liver. Of the other amebas associated with suppurative and inflammatory processes we possess no accurate information establishing their disease-producing function. With this group should be classed the ameba found in serous exudates and in abscesses about the mouth, and the ameboid organisms which have been encountered in the urine. The ameba described by Behla in the sputum of pertussis has not been established as holding any causal relation to the disease.

Among the flagellated mastigophora are a number of parasites occasionally found in man; several of these have been grouped under the name **Cercomonas hominis.** Systematic writers have incorrectly included with this group parasites possessing more than one flagellum. True cercomonads are pear-shaped, 8 μ to 12 μ long, and possess a single flagellum at the anterior end. They are not uncommonly found in stools and probably have no important pathogenic property. The trichomonas group includes several closely allied parasites. The **Trichomonas intestinalis** is 10 μ to 12 μ long, pear-shaped, spiculated at one end, ciliated along a part of one margin, and may have three or four flagella. A similar organism is sometimes observed in vaginal discharges and is called the **Trichomonas vaginalis.**

The **Balantidium coli**[3] is a protozoal parasite, but belonging to a family differing from the cercomonas; it has been shown to be capable

[1] See remarks on the use of anilin dyes, p. 49.

[2] "Jour. Exper. Med.," vol. ii, 1897, p. 529.

[3] Solovieff, "Russki Vratch," vol. i, No. 14. Brooks, "N. Y. Univ. Bull. of the Med. Sci.," vol. ii, Jan., 1902. Strong and Musgrave, "Bulletin Johns Hopkins Hospital," Feb., 1901. Solojew, "Centralbl. f. Bakt.," Abt. I, 1901, xxix, 821–831, 849–860. Klimenko, "Ziegler's Beitrage," 1903, Bd. 33, p. 281. Janowski, "Zeit. f. klin. Med.," Bd. 32, p. 415. Ehrnrooth, "Zeit. f. klin. Med.," Bd. xlix, p. 321.

of producing disease in man. The organism is ovoidal, slightly broader at the anterior end, and measures 50 μ to 100 μ in length and 40 μ to 60 μ in breadth. A funnel-shaped opening (peristome) is situated in the anterior end; the macronucleus is reniform and the micronucleus globular. The motility of the parasite depends upon the activity of the long cilia that cover it. About 100 cases of diarrhea or dysentery believed to be due to the balantidium have been recorded. That the parasite may enter the mucosa, and even the muscularis, of the intestine, has been abundantly shown. Necrotic foci, hemorrhagic areas, and irregular ulcers are found in the colon. The parasite has been observed in the lymphatics of the intestinal wall and in the pus from an hepatic abscess.

Most of the **trypanosomiases** are diseases of lower animals, but one occurs in man; all are due to organisms of the trypanosomida group.[1] The *Trypanosoma lewisi* is quite common in rats, often without producing any symptoms. Nagana, surra, mal de caderas, and dourine are affections usually occurring in the horse and due to the *Trypanosoma brucei*, *Trypanosoma evansi*, *Trypanosoma equinum*, and *Trypanosoma equiperdum* respectively. Galzeikte is a disease of bovines due to the *Trypanosoma theileri*. Trypanosomes have also been found in birds, reptiles, batrachians, and fish. Human trypanosomiasis is due to the **Trypanosoma gambiense,** a flagellate parasite 15 μ to 30 μ long, 1.5 μ to 2 μ thick; one margin of the parasite is outlined by an undulating membrane, along the free margin of which is attached a flagellum arising from the centrosome posteriorly and projecting as a free lash from the anterior end of the parasite (see Fig. 99, p. 184). The disease is inoculated by a tsetse-fly—the Glossina palpalis—and has been communicated to a number of mammalia. In man the organism appears to remain as a blood parasite for a considerable length of time, eventually entering the cerebrospinal fluid and giving rise to a fatal disease called **sleeping sickness** (African lethargy).

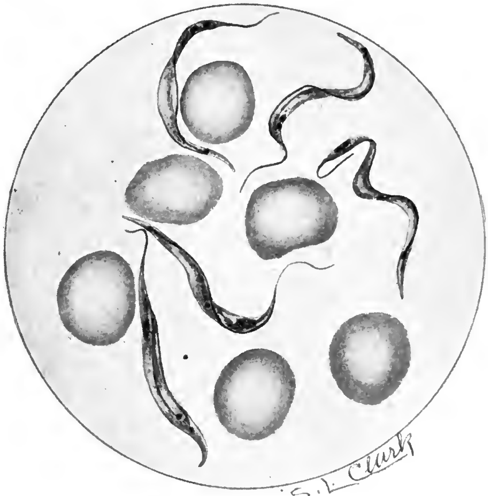


FIG. 98.—TRYPANOSOMA LEWISI.
Laveran and Mesnil stain: 1/12 in. homo im., 1 in. oc.

[1] Laveran and Mesnil, "Trypanosomes et Trypanosomiases," Paris, 1904. An enormous amount of literature has recently accumulated concerning these parasites. The interested reader will find the most important articles in the recent files of the "Jour. of Tropical Med.," "Brit. Med. Jour.," The Royal Society Reports of the Sleeping Sickness Commission, "Centralbl. f. Bakt.," Bd. xxiv, xxv, and xxvi, "Annales de l'Inst. Pasteur," and "Bulletin de l'Inst. Pasteur."

Morbid Anatomy.—In the earlier stages there may be no noteworthy alterations; neuralgias, edemas, skin eruptions, enlargement of the lymph-nodes, and emaciation with irregular fever may be present. After the affection attacks the central nervous system Mott has shown that a meningo-encephalitis results. Frequently terminal infection by a streptococcus (hypnococcus of Castellani) produces a definite meningitis found at autopsy.

The possible relation of these organisms to the spirochætæ has been mentioned on page 172.

Coccidiosis is a condition produced by invasion of cells—mostly epithelium—by parasites called coccidia. They are particularly prone to infect the biliary passages; coccidial cysts of the liver are frequent in some of the lower animals, especially the rabbit, and are occasionally observed in man. Once within the epithelial cell the parasite increases in size and divides into a number of small, crescentic bodies grouped around a central portion of inert, residual protoplasm; the cell so dividing is called a *schizont*, the process is termed schizogony, and the resulting sporules are the *merozoites*. This method of increase Doflein calls *multiplicative reproduction*. The actively motile merozoites enter new epithelial cells and repeat the process of schizogony. *Propagative reproduction* (Doflein) occurs through the evolution of sexual stages, certain of the merozoites being converted into sexually mature organisms, called *gametes*. A merozoite enlarges, its protoplasm becomes granular (*macrogametocyte*) and finally maturates, becoming the female cell or *macrogamete*. The male cell is also developed from a merozoite; it is smaller than the female and the protoplasm is clearer; its nucleus divides, the resulting chromatin masses collecting at the periphery and eventually passing out as flagellate bodies. The male cell is called the *microgametocyte* and the extruded motile flagella containing chromatin particles are *microgametes*. The flagellated microgamete at once seeks and enters a receptive eminence developed on the surface of a macrogamete, with the nucleus of which it fuses, completing the act of fertilization; the resulting body is called the *zygote*. This sexual reproduction is called *sporogony*, which proceeds as follows: The fertilized cell (*zygote*), possessed of active movement, is called, during its migration, the *ookinet;* when it comes to rest and acquires a capsule it becomes the *oocyst*, *copula*, or *sporont*, and is composed of a central nuclear mass surrounded by protoplasm and enclosed in a shell which, in some coccidia, is extremely resistant. By proliferation of the nucleus and separation of the protoplasm, four *sporoblasts* are developed. Each sporoblast acquires a protecting membrane and is now called a *sporocyst;* by segmen-

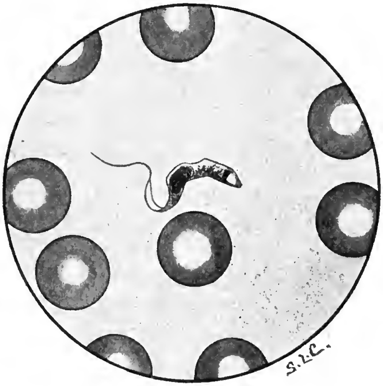


FIG. 99.—TRYPANOSOMA GAMBIENSE IN HUMAN BLOOD.
From specimen prepared by Dr. Jimenez and kindly presented to the writer.

tation of its nucleus two *sporozoites* are developed in the sporocyst. The latter bodies are sickle-shaped, possess a relatively high degree of resistance, and constitute a resting stage in the cycle of the parasite. Entering a new host, the capsule of the sporocyst is digested or ruptures, the contained sporozoites are liberated, and, if conditions are favorable, at once attack the somatic cells.[1] Zoologists propose to classify coccidia according to the number of sporozoites contained in the sporocyst developed by each particular organism.

Probably the best known of the coccidia is the **Coccidium[2] oviforme,** a common parasite in the liver of the rabbit and occasionally causing coccidial cysts in the human liver. Such cysts have the appearance of semisolid or partly caseous nodules resulting from proliferative and necrotic changes in the epithelial cells of the bile-duct. The masses vary in size and are frequently encapsulated. The oocyst of the Coccidium oviforme is 25 μ to 30 μ long and about half as wide. The intracellular position of the parasite in some of its stages can frequently be seen in scrapings, fragments, or sections from such cysts. A skin affection due to a coccidium has been described. The coccidial origin of tumors has been strongly advocated by a number of observers; as the demonstration seems to me to be incomplete, I have not incorporated the various views that have been advanced.[3]

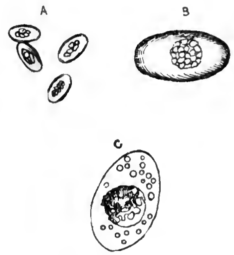


FIG. 100.—COCCIDIUM OVIFORME FROM THE HUMAN LIVER.—(*After Leuckart.—Gould.*)

A. × 200 diameters. B, C. × 800 diameters.

There are a number of morbid conditions of obscure or undetermined etiology in some of which parasites believed to be protozoa have been described. Where the evolutionary cycle of the parasite has not been worked out it is impossible to say exactly to which group the alleged organism belongs. Since the observations of Van der Loeff,[4] Pfeiffer,[5] and Guarnieri[6] numerous investigators have patiently continued attempts to establish the parasitic origin of smallpox. That this disease is due to a living contagion is clearly indicated by its clinical and epidemiologic characters. The evidences of its protozoan origin have recently been urged by Councilman[7] and his students, who have verified and extended previous observations. The bodies believed to be parasites are included in the epithelial cells, some forms being found in the protoplasm and others within the nuclei. Calkins[7] believes that the known data may be so correlated that the developmental cycle of the parasite can, in part at least,

[1] See diagram illustrating the cycles of the Plasmodium malariæ, p. 188.

[2] Zoologists have recently adopted the term eimeria as the correct name for the coccidium; I shall, however, adhere to the older nomenclature. Tyzzer, "Jour. of Med. Research," April, 1902.

[3] Schüller, "Centralbl. f. Bakt.," Dec. 12, 1904, p. 547.

[4] "Monatsch. f. prakt. Derm.," 1887, Bd. iv, p. 189.

[5] Ibid., p. 435.

[6] "Arch. per le Sci. Med.," Tome xxvi, p. 403.

[7] "Jour. of Med. Research," Feb., 1904, vol. xi, No. 1, pp. 1 to 361, with full bibliography. Howard and Perkins, "Jour. of Med. Research," Oct., 1904. Ewing. "Jour. of Med. Research," Nov., 1904, and Feb., 1905. De Korte, "Lancet," Dec. 24, 1904, and "Practitioner," Jan., 1905. Bosc, "C. R. Soc. de Biol.," t. v, p. 1178, also "Centralbl. f. Bakt.," Aug. 26, 1904, p. 630, and Sept. 23, 1904, p. 59.

be followed. The name **Cytoryctes variolæ** has been given to the organism, and it is thought that the difference between vaccinia and variola depends upon modifications in the same parasite. Mallory[1] describes a protozoa-like body found in four cases of scarlet fever. Negri[2] has found a parasite of an undetermined nature occupying certain ganglion cells of the central nervous system in hydrophobia. Wright, and also Marzinowsky and Bogrow,[4] have extended previous knowledge and made additional observations on the parasitology of tropical ulcer and Oriental boil. Tietze[5] has found a protozoon in a parotid tumor, and suggests that the parasite may be the cause of the obscure enlargement of the parotid gland in the condition called Mikulicz's disease.

The scope of this work does not permit an exhaustive review of the organisms to which reference has been made in the preceding paragraph. In some of the diseases investigations are incomplete and the results not corroborated by a sufficient number of observers to justify final judgment.

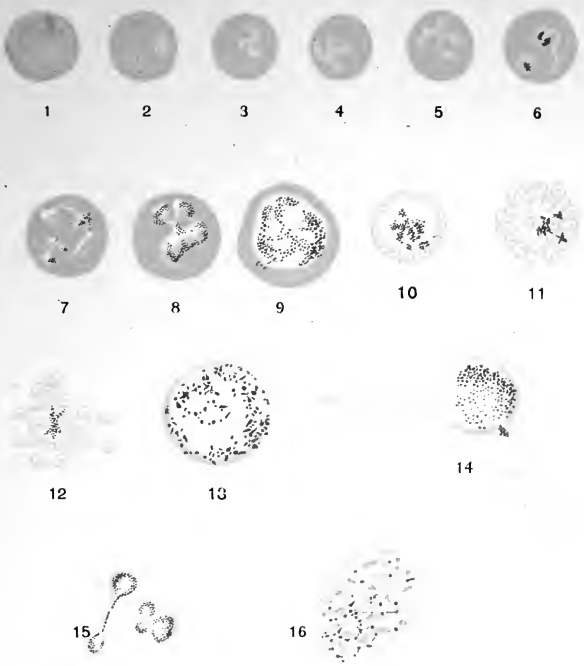
Probably the most important of the sporozoa are the **Hæmosporidia,** which, as Doflein aptly observes, are protozoa that have acquired a parasitic life adapted to existence within the erythrocytes. A number of these organisms affect animals other than man, giving rise to the malaria of birds, fish, etc.

The most important of the hæmosporidia is the parasite causing human malaria, called the Hæmatozoon malariæ, Hæmatomonas malariæ, Hæmamœba malariæ, but probably best known as the **Plasmodium malariæ.**[6] During the presence of the parasite in the circulating blood a large part of its existence is spent within the red blood-cell. In man multiplicative reproduction (see p. 184) alone occurs; propagative reproduction (see p. 184), or the sexual cycle of evolution, takes place in the body of the mosquito (Anopheles). So far as is known, no other gnat can serve as a host for the Plasmodium malariæ. There are three types of parasites observed in the three forms of human malaria; the parasite of tertian fever completes its cycle of development in forty-eight hours, the plasmodium causing quartan malaria requires seventy-two hours for the production of sporulation, and in the so-called estivo-autumnal or pernicious malaria, the parasite—Plasmodium præcox—varies in the length of time necessary for its complete evolution.

The most frequent form of malaria is that produced by the tertian parasite **Plasmodium vivax** (Plate II), the evolution of which may be traced by repeated examinations of the peripheral blood, beginning immediately after a paroxysm and continuing at intervals of two to four

[1] "Jour. of Med. Research," Jan., 1904, p. 483.
[2] "Zeit. f. Hyg. und Infektkrank," 1903, xliv, p. 507.
[3] "Jour. of Med. Research," 1903, vol. x, p. 472.
[4] "Virchow's Archives," 1904, Bd. 178, p. 112.
[5] "Mittheil. a. d. Grenzgebiet. de Med. u. Chir.," 1904, xiv, No. 3.
[6] All the important literature bearing on malaria may be traced from the references given by DaCosta in his "Clinical Hematology," second edition, 1905, pp. 445 to 472. See also Doflein, "Lehrbuch der Protozoenkunde," II Auflage, Jena, 1909. Schaudinn, "Arbeit. a. d. Kaiser Gesundheitsammte," 1902, Bd. xix, and 1903, Bd. xx. Stephens and Christophers, "Practical Study of Malaria," London, 1903. Nnttall's exhaustive studies on the biology of the Anopheles will be found in the "Jour. of Hygiene," 1901, vol. i, and 1902, vol. ii. Craig, "Amer. Med.," Oct. 29, 1904, on "Latent and Masked Malarial Infections."

PLATE II.



THE TERTIAN PARASITE.

(From Da Costa's "Clinical Hematology.")

1. *Normal erythrocyte.*
2, 3, 4, 5. *Intracellular hyaline forms.*
6, 7. *Young pigmented intracellular forms.* In 6 two distinct parasites inhabit the erythrocyte, the larger one being actively ameboid, as evidenced by the long tentacular process trailing from the main body of the organism. This ameboid tendency is still better illustrated in 7, by the ribbon-like design formed by the parasite. Note the delicacy of the pigment granules, and their tendency toward peripheral arrangement in 6, 7, and 8.
8. *Later developmental stage of 7.* In 7, 8, and 9 enlargement and pallor of the infected erythrocyte become conspicuous.
9. *Mature intracellular pigmented parasite.*
10, 11, 12. *Segmenting forms.* In 10 is shown the early stage of sporulation—the development of radial striations and peripheral indentations coincidentally with the swarming of the pigment toward the center of the parasite. The completion of this process is illustrated by 11 and 12.
13. *Large swollen extracellular form.* Note the coarse fused blocks of pigment. (Compare size with that of normal erythrocyte, 1.)
14. *Flagellate form.*
15. *Shrunken and fragmenting extracellular forms.*
16. *Vacuolation of an extracellular form.*

NOTE.—The original water-color drawings were made from fresh blood specimens, a Leitz $\frac{1}{12}$-inch oil-immersion objective and 4 ocular, with a Zeiss camera-lucida, being used.

(E. F. FABER, *fec.*)

hours until the cycle is completed. If a drop of the fresh blood be prepared for examination (see Technic of Blood Examination Chapter I, Part III) during or immediately after the paroxysm, the earliest stages in the evolution of the plasmodium may readily be followed. A magnification of about 1000 diameters ($\frac{1}{12}$-inch oil immersion) will be found convenient, but not absolutely necessary, as the discoverer of the parasite, Laveran, commended a magnification of 600 ($\frac{1}{6}$-inch or $\frac{1}{8}$-inch objective, with a good eye-piece). Carefully focusing on a part of the field in which the red blood-cells are thinly spread, the slide is slowly moved, a close watch being kept for pale bodies in the corpuscles, or for pale corpuscles, in which the parasite is to be sought. The iris diaphragm with substage condenser should be partly closed, so as not to flood the field with light sufficient to obliterate the finer details. In varying numbers of the red blood-cells transparent (hyaline) bodies with fairly sharp margins can readily be found. The smallest of these does not exceed 2 μ in diameter, and if carefully watched its form will be seen constantly changing. In the earliest stage it is without pigment and resembles the so-called vacuole or hydropic spots sometimes seen in erythrocytes, from which, however, it is readily differentiated by the rapid ameboid movements of the plasmodium. In another specimen of blood collected three or four hours later the intracellular parasites will be found very much larger, the ameboid movement more active, the pseudopodia appearing and disappearing constantly. Sometimes the protoplasmic projections, thrust through the interior of the red cell, meet, imprisoning part of the hemoglobin content in the interior of the parasite. Toward the end of the first twenty-four hours following a paroxysm, pigment begins to appear in the interior of the parasite and the plasmodium becomes proportionately easier to recognize. This pigment is composed of fine brownish-yellow granules, most abundant near the periphery of the organism and in constant motion. If the slide be cooled, the vibrations of the pigment become slower and eventually cease. By this time the parasite occupies about half of the erythrocyte. During the evolution of the plasmodium the affected red cell becomes slightly swollen and progressively paler. In from four to six hours before the approaching paroxysm, the parasite has attained its maximum size and the process of sporulation begins. The pigment granules collect toward the center, the periphery of the parasite is outlined by numerous short arcs the convexity of which is toward the periphery of the erythrocytes, and from the points where these arcs meet, faint lines are projected toward the centrally collected mass of pigment. As this stage is completed the parasite is divided into fifteen or twenty oval or pyriform segments, the apices of which are directed toward the inactive pigment in the center. As now seen, the remains of the swollen erythrocyte are indistinct and the radiating spores present the characteristic *rosette* or daisy form. With the completion of sporulation the red cells containing the parasites rupture, the liberated young plasmodia are freed in the blood-plasma and at once enter red cells. The liberated pigment is taken up by the phagocytes, particularly the leukocytes, but also by phagocytic endothelial cells.

A careful examination of the blood will show that in a number of the infected red cells sporulation does not occur, and that in an earlier stage in the evolution of the parasite it escapes from the host cell. This

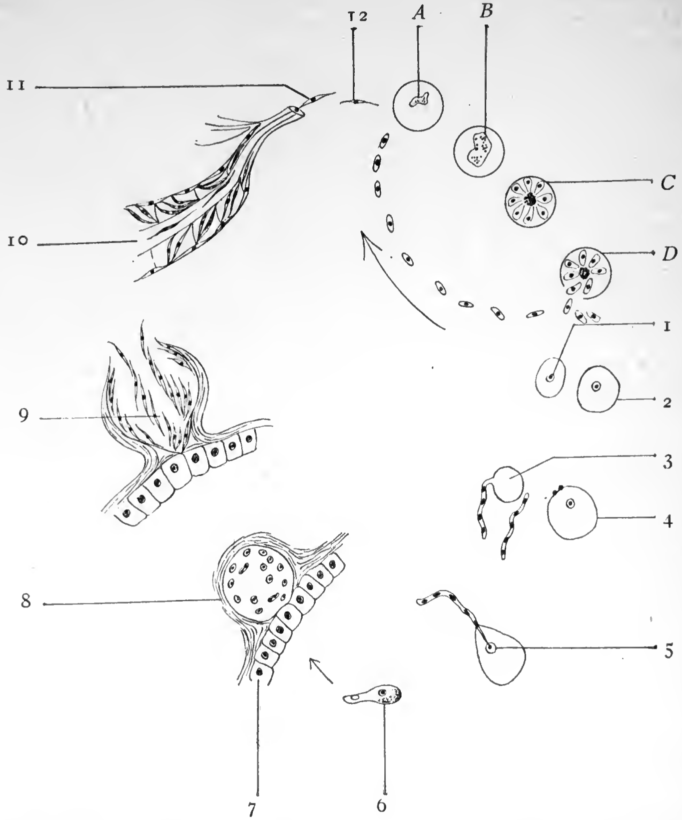


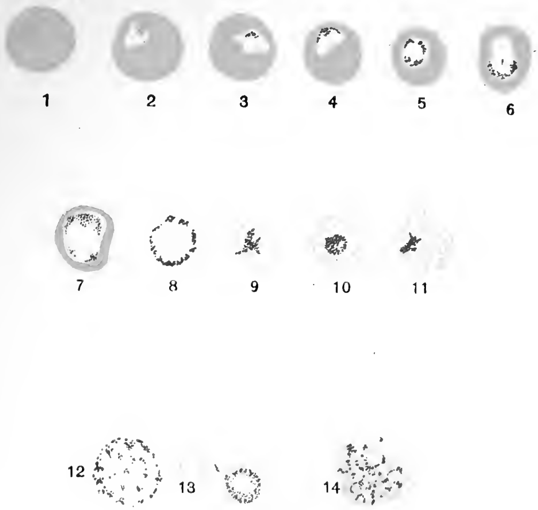
FIG. 101.—DIAGRAMMATIC REPRESENTATION OF THE LIFE CYCLE OF THE PLASMODIUM MALARIÆ.—(*Modified and redrawn after Clarke.*)

[The letters refer to the stages of schizogony and the figures to sporogony.]

A. Hyaline intracorpuscular body called by Lankaster the amebula, the earliest stage of the parasite within the red cell.
B. Later stage of A, showing beginning formation of pigment. A and B are stages in the growth of the merozoite, and with C constitute the changes in the schizont during the process of schizogony.
C. Sporulating intracellular parasite; daisy or rosette form; pigment in center.
D. Ruptured cell liberating sporules or merozoites,some of which return to red cells, as indicated by the arrow, and repeat this process of schizogony or multiplicative reproduction. Other merozoites after intermediary stages develop into gametes.

1. Microgametocyte or male element.
2. Macrogametocyte or female element.
3. Microgametocyte from which two microgametes are being given off (exflagellation); one microgamete has separated. The dots in the microgamete imperfectly represent contained particles of chromatin.
4. Macrogamete which has just completed maturation by extruding part of its nuclear substance represented by the dots above the cell.
5. Fertilization of the macrogamete by the entrance of the microgamete through the receptive eminence. This body is now a zygote.
6. Motile body developed from the zygote and called the ookinet, which, as indicated in the diagram, is about to penetrate the walls of the mid-intestine of the mosquito.
7. Epithelium of mid-intestine of mosquito.
8. Oocyst in the wall of the gnat's intestine; nuclear division has occurred.
9. Matured oocyst, or sporocyst, which has ruptured, permitting the sporozoites to escape into the body-cavity of the mosquito, from which they pass to the salivary gland of the insect.
10. Part of veneno-salivary gland of the mosquito; numerous sporozoites are present in the cells of the gland and in the duct to which the pointer leads.
11. Sporozoite escaping from the gland duct.
12. Free sporozoite ready to enter the erythrocyte of a new host.

PLATE III.



THE QUARTAN PARASITE.

(From Da Costa's "Clinical Hematology.")

1. *Normal erythrocyte.*
2. *Intracellular hyaline form.*
3. *Young pigmented intracellular form.* Note the coarseness, dark color, and scantiness of the pigment granules.

4, 5, 6, 7. *Later developmental stages of 3.* Note the peripheral distribution of the pigment in all the parasites from 3 to 8. (Compare size and color of the erythrocytes in 5, 6, and 7 with 7, 8, and 9, Plate I.)

8. *Mature intracellular form.* Note that the stroma of the erythrocyte is no longer demonstrable.

9, 10, 11. *Segmenting forms.* In 9 are shown the characteristic radiating lines of pigment. (Compare with 10, 11, and 12, Plate I, and with 10, 11, and 12, Plate III.)

12. *Large swollen extracellular form.* (Compare with 13, Plate I.)
13. *Flagellate form.* (Compare with 14, Plate I.)
14. *Vacuolation of an extracellular form.*

(E. F. FABER, *fec.*)

step is the first stage in the evolution of the sexual life of the plasmodium, and it is now prepared to enter the tissues of another host. Certain of these extracellular pigmented forms (gametocytes) are macrogametocytes and others microgametocytes, the later evolution of which occurs in drawn blood only. A mosquito of the genus Anopheles is the host in which the subsequent development of the parasite occurs. When the blood enters the stomach of the mosquito, the microgametes derived from the microgametocytes enter and fecundate the macrogametes, which become ookinets. These bodies, endowed with motility, penetrate the mucosa of the mid-intestine of the gnat and become oocysts in the intestinal wall. By changes already described (see p. 184) the oocyst develops into a sporocyst and ruptures into the body cavity (cœlom) of the mosquito; the liberated sporozoites eventually reach the salivary gland of the gnat and enter the venom duct, from which, when the insect next feeds, they are inoculated into the human host. The formation of flagellate bodies does not occur in the circulating blood, but in properly prepared mounts, made just before the malarial paroxysm, the formation of flagella may be seen between fifteen and thirty minutes after the blood is drawn. The pigment of the macrogametocyte becomes actively disturbed, and from the periphery of the plasmodium pointed or bulbous flagella, often 20 μ to 30 μ in length, are thrust violently into the surrounding plasma and may often be seen lashing contiguous cells; a flagellum loosened from the microgametocyte may sometimes be seen free among the red cells. In properly stained specimens each flagellum is found to contain more or less chromatin, either collected in the bulbous extremity or distributed along the center of the filament.

The development of the quartan parasite, **Plasmodium malariæ,** follows closely that already outlined as occurring in the tertian, but shows sufficiently distinctive characters to enable the observer to differentiate the two organisms. The hyaline intracellular form, in its early stage, is indistinguishable from that of the tertian parasite. By the time pigmentation has appeared certain differentiating points may be recognized. The pigment is coarser, darker, and sluggish; the outlines of the parasite are sharper, and as it grows older its movement becomes less active. The infected red cell shrinks and grows darker, occasionally taking on the so-called "brassy" hue. The protoplasm of the parasite appears denser and more grayish than that of the tertian form. The tertian parasite produces sixteen to twenty-four segments, the quartan eight to twelve The former requires forty-eight hours and the latter seventy-two hours for completing the hemal cycle. The asexual cycle of the quartan parasite follows in essential detail that outlined for the tertian.

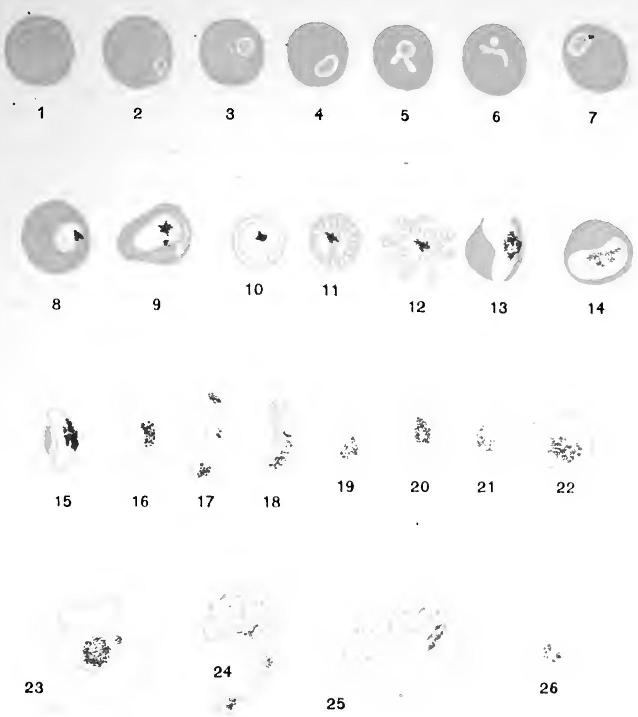
The estivo-autumnal parasite—**Plasmodium præcox**—varies in the length of time necessary for its developmental cycle. While all stages in the evolution of the quartan parasite may readily be obtained in the peripheral blood, sporulating forms of the estivo-autumnal organism are never present peripherally. In the earlier stages the intracellular hyaline body is not unlike similar forms seen in tertian and quartan parasites. Soon, however, ameboid rings or signet-ring shapes are found, and rapid changes from the ring to a flattened disc are regarded as characteristic of this organism. The pigment is fine and never abundant. Segmentation may be seen in the splenic blood drawn during life, or in the marrow postmortem.

The segmenting forms are smaller than in the other plasmodia, although following in a general way the rosette shape of the tertian parasite. After a week or ten days the most characteristic evidence of estivo-autumnal infection becomes demonstrable by the appearance in the peripheral circulation of **crescent, round,** and **ovoid bodies** usually contained in the thin shell of the now colorless erythrocyte. These crescents resemble a moon in the first quarter with the points of the horns slightly rounded, and measure 5 μ to 8 μ in length. The pigment is usually centrally placed. The ovoid forms are commonly smaller than the crescents and part of the host cell can nearly always be shown about them. It is evident that these structures are gametes. In the proper condition the formation of flagella may readily be recognized.

TABULATED DATA USEFUL IN DIFFERENTIATING THE PARASITES FOUND IN MALARIA.

	Tertian Parasite.	Quartan Parasite.	Estivo-autumnal Parasite.
Hyaline body,...	Outline indistinct; actively ameboid	Outline distinct; ameboid movement slow.	Small, sharply outlined, active; ring-shape, common.
Pigment granules,	Fine, light-brown, active.	Coarse, dark-brown, sluggish, peripherally placed.	Very fine, scanty, motile or stationary.
Size of mature parasite,.......	As large or larger than erythrocyte, 7 μ to 9 μ.	Smaller than erythrocyte, 5 μ to 6 μ.	Usually very much smaller than erythrocyte, 2 μ to 6 μ.
Sporulation segments, ...	15 to 24. Usually in two rows or irregularly placed.	6 to 12. Arranged symmetrically around central pigment.	6 to 15 or more. Symmetrically or irregularly placed.
Preflagellate form, ...	Swollen, pigmented body 9 μ to 12 μ in diameter.	Swollen, pigmented body, 5 μ to 8 μ in diameter.	Spherical, pigmented body, 4 μ to 6 μ in diameter. (Derived from crescents.)
Erythrocyte,.....	Becomes pale and greatly swollen.	Becomes dark in color and shrunken.	Greenish or "brassy" in color. Often crenated.
Cycle,..........	48 hours. Sporulating forms not abundant in peripheral blood.	72 hours. Sporulating forms fairly numerous in peripheral blood.	24 or 48 hours. Sporulating forms in spleen and bone-marrow; not in peripheral blood.

PLATE IV.



THE ESTIVO-AUTUMNAL PARASITE.

(From Da Costa's "Clinical Hematology.")

1. *Normal erythrocyte.*
2, 3. *Young hyaline ring-forms.*
4, 5, 6. *Intracellular hyaline forms.* In 4 the parasite appears as an irregularly shaped disc with a thinned-out central area. In 5 and 6 its ameboid properties are obvious.
7. *Young pigmented intracellular form.* Note the extreme delicacy and small number of the pigment granules. (Compare with 6, Plate I, and with 3, Plate II.)
8, 9. *Later developmental stages of 7.*
10, 11, 12. *Segmenting forms.*
13, 14. *Crescentic forms at early stages of their development.*
15, 16, 17, 18, 19. *Crescentic forms.* In 15 and 19 a distinct "bib" of the erythrocyte is visible. Vacuolation of a crescent is shown in 18, and polar arrangement of the pigment in 17.
20. *Oval form.*
21, 22. *Spherical forms.*
23. *Flagellate form.*
24. *Vacuolation and deformity of a spherical form.*
25. *Vacuolated leucocyte apparently enclosing a dwarfed and shrunken crescent.*
26. *Remains of a shrunken spherical form.*

(E. F. FABER, *fec.*)

In all forms of the disease the so-called **malarial paroxysm**—which in typical cases is characterized by the occurrence of chills, fever, and sweating—develops at the time which corresponds to the occurrence of sporulation in the parasite. The symptoms must depend upon the presence of some poison, although all attempts at the isolation of such a body have been disappointing. The active hemolysis that accompanies all forms of the disease necessarily throws great stress upon the blood-forming organs, and, by the liberation of pigment, gives rise to deposits which are particularly evident in the liver and spleen. The changes in the organs are largely dependent upon the duration of the affection. Even in recent cases leukocytes containing pigment are of common occurrence and of great diagnostic value; in older cases the number of these cells is sometimes most striking. In the acuter cases of malaria the hepatic changes resemble those seen in certain bacterial infections; the organ is swollen, the epithelium granular, sometimes fatty, areas of focal necrosis occur and the biliary passages are not infrequently the seat of a well-marked catarrhal cholangitis. In more chronic cases the pigmentation is marked (slate-colored liver), the fibrous tissue increased, and not infrequently a moderate degree of red atrophy is present. In both acute and chronic cases plasmodia and pigment may be found in the capillaries. The spleen in acute cases is soft, the pulp dark, the endothelium proliferating and phagocytic, and parasites abundant both within and without the red blood-cells. In chronic malaria the spleen is enlarged (ague-cake), firm, cuts with resistance, and is of a slaty hue. The fibrous tissue is enormously increased. In acute malaria the renal epithelium is granular and sometimes fatty; the kidneys are intensely congested, occasionally edematous, and soft. Ewing and others have demonstrated plasmodia in the Malpighian tufts. In chronic malaria a moderate diffuse nephritis with some increase in the fibrous tissue may be present. The bone-marrow shows more or less hyperplasia and pigmentation and commonly contains demonstrable numbers of plasmodia, many of which are sporulating. Sometimes the marrow reverts to the embryonal type, while in other instances the proliferative changes are less marked. The capillaries of the gastro-intestinal mucosa may be packed with parasites, and it is possible that this explains the marked gastro-intestinal symptoms present in some cases. The cerebral symptoms seen in malaria may be attributed to massing of the parasites either generally or locally, or to the toxemia. The brain and cord are usually edematous or hyperemic; and minute hemorrhages may be present; structural changes are recognizable in the ganglion cells, which commonly manifest more or less chromatolysis and granular changes in the dendrites and neurofibrils.[1]

Other protozoal parasites that might with propriety be described as hemosporidia have been reported. Löwit[2] believes he has demonstrated the protozoal origin of leukemia. Graham[3] and Eberle[4] attribute dengue to parasites resembling those of malaria. The first-named observer states that the Culex fatigans is the mosquito in which the sexual cycle of the parasite is completed and by which the disease is disseminated.

[1] For exhaustive review of the pathologic anatomy of malaria fever, see Ewing, "Jour. Exper. Med.," vol. vi, p. 119.

[2] "Die Leukämie als Protozoeninfektion," Wiesbaden, 1900.

[3] "Medical Record," 1902, vol. xli, p. 204.

[4] "New York Med. Jour.," Dec. 24, 1904, p. 1207.

VERMES.

The **vermes** (worms) of importance in human pathology belong to (1) trematodes, (2) cestodes, or (3) nematodes.

Under the name **distomatosis** or **distomiasis** is included a number of affections occurring in man and lower animals and due to trematodes, also called flukes. Stiles[1] suggests that the following clinical forms of distomatosis be recognized: (*a*) Ophthalmic distomatosis,[2] about which we have little accurate information, as the condition is exceedingly rare; (*b*) pulmonary distomatosis, or parasitic hemoptysis, with which should be mentioned cerebral distomatosis, usually secondary to pulmonary lesions; (*c*) hepatic distomatosis; (*d*) pancreatic distomatosis; (*e*) intestinal distomatosis; (*f*) venal distomatosis.

Pulmonary distomatosis,[3] also called parasitic hemoptysis, is due to the *Paragonimus westermanii*, also called the Distoma westermanii, Distoma ringeri, Distoma pulmonale, etc. The adult parasite is 8 mm. to 20 mm. long, 4 mm. to 8 mm. broad, and 2 mm. to 5 mm. thick. The eggs are oval, 80 μ to 100 μ long, 50 μ to 90 μ broad, and possess a yellowish shell; when hatched they give rise to a *miracidium*, of which we possess little accurate information. The method by which infestation in man occurs is not known; it has usually been held that the parasite enters with the ingesta, but recent more accurate knowledge of allied parasites suggests the possibility of transcutaneous infection. In man the disease is characterized by bronchial and pulmonary symptoms and the expectoration of dirty red, or reddish-brown sputum containing the eggs, of which twelve thousand may be discharged daily. Hemoptysis occurs in most cases. At autopsy the parasites are found in the bronchi and in irregular caverns in the pulmonary tissues. The cavities are marginated by areas of induration associated with more or less interstitial pneumonia and peribronchial thickening. Metastasis to the brain is occasionally seen. It is characterized by the occurrence of areas of softening the peripheries of which are infiltrated by mononuclear cells; eggs are present in the affected vessels. Cirrhosis of the liver due to the ova is sometimes found. The diagnosis of pulmonary distomatosis is made by finding the eggs in the sputum.

Hepatic distomatosis may be due to any one of at least five species of parasite, all of which are members of the *fasciolidæ*. The *Fasciola hepatica* (common liver fluke, Distoma hepaticum) is 18 mm. to 35 mm. long, and 8 mm. to 15 mm. wide; the surface is spiculated, the apices of the spines being directed backward. The yellowish-brown eggs are oval, 125 μ to 150 μ long, and 70 μ to 80 μ thick; they are present in the feces during the active stages of the disease. The *Dicrocœlium lanceatum* is a much smaller liver fluke and rarely affects man.

The *Opisthorchis felineus* (Distomum lanceolatum, Distomum sibi-

[1] I shall take some liberties with, but in a general way will follow, the admirably outlined plan suggested by Charles Wardell Stiles, Hygienic Laboratory Bulletin, No. 17, 1904. From the bibliography given in that publication the literature of the subject may be followed.

[2] I shall make no further reference to this affection; those interested may consult Stiles' monograph.

[3] Stiles, "Proceed. Path. Soc. of Phila.," Feb. 1, 1901, vol. iv, p. 61. Taniguchi, "Archiv. f. Psychiatrie und Nervenkrank.," vol. xxxviii, 1904. Mackenzie, "Jour. Amer. Med. Assoc.," April 30, 1904, p. 1133.

riscum) is 8 mm. to 15 mm. long, 1.25 mm. to 2.5 mm. broad, flat and lanceolate and without surface spines. The eggs are oval, 30 μ to 36 μ by 11 μ to 15 μ, with an operculum at the smaller pole. The *Opisthorchis noverca* is 9 mm. to 12 mm. long, 2 mm. to 5 mm. broad, lanceolate and with spiculated skin; the eggs are oval, 34 μ by 19 μ to 21 μ. The *Opisthorchis sinensis* is 10 mm. to 20 mm. long, 2 mm. to 5 mm. broad, lanceolate or oval and without spines. The dark brown, oval eggs are 27 μ to 30 μ by 15 μ to 17 μ.

In hepatic distomatosis the liver is enlarged, the capsule thickened, the interstitial tissue increased (cirrhosis), and the bile-ducts dilated and inflamed. The parasites and eggs are usually demonstrable in the biliary passages. The hepatic cells show granular or fatty changes, the periphery of the lobule is frequently infiltrated by round cells, and areas of necrosis are usually present.

Of **pancreatic distomatosis** but little is known. It is caused by the migration of flukes into the pancreatic duct and is characterized by dilatation and inflammation of the ducts, necrosis of the pancreatic tissue, interstitial pancreatitis, and sometimes areas of hemorrhage. The condition may be produced by some of the flukes causing hepatic distomatosis.

Intestinal distomatosis is a manifestation of the irritant action of flukes or their eggs upon the intestinal mucosa. Of the relatively large number of trematodes that are occasionally found in the intestine but little is known as to their special action on this part of the alimentary canal. Stiles describes the parasites found, and those interested may consult his paper.

FIG. 102.—FASCIOLA HEPATICA.

The trematodes to which reference has been made in the preceding paragraphs are flat, oblong or conical, hermaphrodite worms possessing two suckers (hence the name di-stoma); the anterior or oral sucker is in front of the mesially placed second sucker, called the acetabulum. The oral sucker leads into a short tube (pharynx and esophagus) which, anterior to the acetabulum, bifurcates, giving rise to two convoluted tubules, one of which traverses each side of the parasite, and terminates as a blind sac in the posterior part of the worm. There are usually two round or lobate testes, one on each side, and an extremely complex uterus and ovisacs in which the developing eggs may be detected. The parasite possesses no anus, although an excretory pore may be recognized. The hatched eggs develop into a miracidium, for the further evolution of which a second host is necessary.

Venal distomatosis,[1] also called endemic or parasitic hematuria, bilharzia disease, Bilharzia hæmatobia infection, Bilharzia distomatosis, or Bilharziosis, is a disease affecting the bladder, rectum, portal system, and liver, and caused by the *Schistosoma hœmatobium* (Bilharzia hæma-

[1] See foot-note, p. 181. Milton, "Lancet," March 28, 1903. Symmers, "Jour. of Path. and Bact.," December, 1903. Douglas and Hardy, "Lancet," Oct. 10, 1903. Rafferty, "Med. Record," June 4, 1904. Rankin, "Brooklyn Med. Jour.," July, 1904. O'Neill, "Boston Med. and Surg. Jour.," Oct. 27, 1904. Sandwith, "Practitioner," Oct., 1904. Clayton-Greene, "Lancet," Dec. 17, 1904. Kautsky-Bey, "Zeit. f. klin. Med.," 1904, Bd. 52, p. 192. Letulle, "Soc. de Biol.," Paris, April 8, 1905.

tobia, Distoma hæmatobium, blood fluke). Unlike the flukes already described this parasite is not hermaphroditic. The male is 10 mm. to 15 mm. long, 1 mm. wide, the lateral margins curved toward the ventral aspect, forming the canalis gynæcophorus for the reception of the female. The dorsal surface is marked by small warty projections permitting the parasite to cling to vessel walls. The female is 20 mm. long and considerably thinner than the male. The surface is also spiculated; the oral sucker and acetabulum of the male or female are not unlike similar structures in other flukes. The parasites inhabit the portal circulation, and the morbid processes with which they are associated are attributed to the injury produced by the spiculated ova, of which the female produces large numbers; the eggs are oval, 120 μ to 160 μ long, 50 μ to 60 μ broad, with a sharp spine projecting from one end; laterally placed spines, occasionally observed, are thought by Looss to be malformed eggs. During life the eggs are found in the urine and in the feces. Postmortem they are abundant in the vesical wall, rectum, ureter, and liver. Urinary fistula are not uncommon; vesical lithiasis occurs in ten to fifteen per cent. of the cases. The eggs in the bladder wall give rise to a chronic cystitis, to marked connective-tissue proliferation and hypertrophy, and to papillomatous or polypoid growths of the mucosa. The ureters may be as large as the small intestine; hydronephrosis and pyonephrosis occur. When the rectum is involved, the mucosa resembles a rich red velvet, and numerous polypoid papillomas may be present. The liver is usually enlarged and may weigh three kilo. The connective tissue is enormously increased, the incised surface of a peculiar drab color, and, in addition to the cirrhosis, properly prepared sections show the presence of typical eggs or shells, or eggs with lateral spines. Letulle has described a special form of phlebitis due to the parasite.

FIG. 103.—SCHISTOSOMA HÆMATOBIUM, MALE AND FEMALE, THE LATTER IN THE CANALIS GYNÆCOPHORUS OF THE FORMER.—(*After Leuckart.—Gould.*)

The diagnosis of venal distomatosis during life is based on the demonstration of spiculated eggs, particularly in the few drops of bloody urine voided at the end of micturition. An important diagnostic point is the notable increase in eosinophiles usually present. In 50 cases examined by Douglas and Hardy the average percentage of eosinophiles was 38.48. The lowest percentage was 1.3; in rare cases one-half of the leukocytes are eosinophiles. For finding the parasites postmortem, Sandwith recommends that the blood, from the portal vein, be scooped out with a spoon and placed in a glass dish; in the thin layers secured in this way the parasites may readily be recognized. The number of parasites in the portal blood is usually not large, although in one of Sandwith's cases 400 were found.

The second important group of vermes affecting man are the **cestodes** or **tapeworms.** The fully formed adult worm (strobila) consists of a head (scolex), to which are attached the flattened segments (proglottides), of which, in some of the tapeworms, a thousand or more may be joined end to end, forming a band-like body. The neck is usually

composed of immature proglottides. Each fully developed proglottis or segment is hermaphroditic, containing a uterus and its appendages, testicular gland and duct; the sexual opening (genital pore) is located in the margin of the proglottis in the Tæniæ and near the center of the flattened surface of the Dibothriocephalidæ. The head is surmounted by special organs enabling the parasite to attach itself to the intestinal mucosa; the bodies accomplishing this are either *suctorial discs* or *grooves*, or a *rostellum* armed with hooklets; some of the tapeworms are supplied with suctorial discs and also the hooklets. Parasites possessing the latter structure are called armed tapeworms.

Like a number of other animal parasites to which reference has been made, the tapeworms do not complete their development in a single host. Most of the cestodes are adult parasites in man and pass their so-called larval stage in one of the lower animals. The eggs escaping from the human intestine enter another host, in the tissues of which a cyst containing the developing larvæ is produced; man consuming meat containing these parasites, digests the capsule, and liberates the parasite in his own alimentary canal. With regard to the Tænia echinococcus, man occupies the position of host for the larvæ, the adult worm occurring in the dog.

Frequently a tapeworm in the alimentary canal is not evinced by any conspicuous manifestations; in other cases, however, the nutrition of the host is profoundly influenced. The local irritation produced by the worm is usually slight, and an important question has been raised as to whether or not these parasites produce definite poisons. Massineo and Calamida,[1] Faber and Bloch,[2] Isaac and von den Velden,[3] and others believe that in the dibothriocephalus some hemolytic substance is produced, through the action of which the accompanying anemia is brought about. Schauman and Talqvist find that different specimens of the dibothriocephalus are not of equal toxicity, and this may explain why in some cases the worm causes anemia while in others it does not. The following are the important cestodes occurring in man.

Tænia mediocanellata[4] or **saginata,** or **beef tapeworm.** The head is quadrate, 1.5 mm. to 2.25 mm., surmounted by four suckers arranged in a quadrangular outline, in the center of which is a fifth rudimentary sucker or flattened groove; the head is void of hooklets, hence the worm is known as the "unarmed tapeworm." The head is attached to a slender neck varying in length and terminating in the first link, proglottis, zooid, or segment—terms used synonymously. The segments when fully developed are between 8 mm. and 10 mm. broad and about 18 mm. long, and thicker than the proglottides of the tænia solium; like all tapeworms, each segment is hermaphroditic. The genital pores are placed laterally; the uterus shows dichotomous branching more characteristically than the Tænia solium; the number of branches varies, but is approximately fifteen; the segments are commonly thrown off spontaneously, while the Tænia solium rarely sheds a single proglottis. The length of the worm varies greatly; the number of segments may exceed 1000

[1] "Jour. Med. Vet. et Zootech.," Sept., 1901.
[2] "Hospitalstinde Copenhagen," vol. xlvi, No. 36.
[3] "Deut. med. Woch.," 1904, xxx, p. 982.
[4] Braun, "Die thierischen Parasiten des Menschen," 1903. Reiss, "Münch. med. Woch.," Feb. 9, 1904, p. 260.

and the entire worm may measure between four meters and ten meters. The ova constantly appear in the stools, and the segments show the uterus distended with them. Each ovum is ovoid—egg-shaped—with a striated outer membrane and a thick shell; the length is 30 μ and the width 25 μ. The eggs and segments discharged in the feces are ingested by the ox; the larva or juvenile parasite is liberated, and reaches the muscles, for the most part, although it has been observed in the heart, lungs, and liver. At the point of deposit there develops a cyst, varying in size from 2 mm. to 2 cm. in diameter, whitish in color, and oval in outline. In this is the larval worm; the cyst wall is of connective tissue. In this stage the parasite is known as *cysticercus saginata.* Beef rarely contains many such cysts, and their small size not uncommonly causes them to be overlooked. Beef containing the cysts is said to show "measles." It is not known that man suffers from cysticercus saginata.

Tænia solium, also known as the **pork tapeworm, solitary tapeworm,** and **armed tapeworm.** The name Tænia solium, or solitary tapeworm,

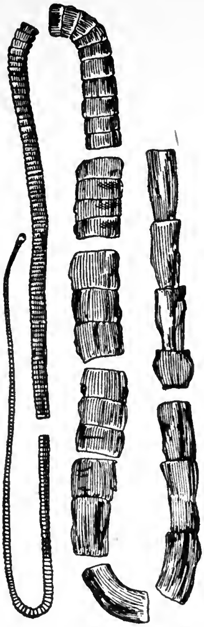


FIG. 104.—TÆNIA SAGINATA.—(*Gould.*)

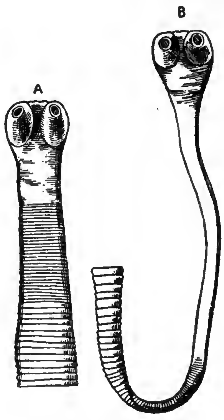


FIG. 105.—CEPHALIC END OF TÆNIA SAGINATA. A. Retracted head. B. Extended head.

is not appropriate, as the pork tapeworm is more commonly multiple than the Tænia saginata; indeed, Leidy regarded the latter as rarely multiple. The adult parasite is a soft, white, band-like worm, rarely over four meters in length. The head is round, 0.5 mm. to 1 mm. in diameter; there are four discoid or cup-like suckers and a centrally placed papilla, proboscis, snout, or rostellum, surmounted by two rows of hooklets, each row having from twelve to fourteen hooklets; the hooklets of the inner row are the larger. The neck is very thin, about 2.5 cm. in length, terminating in the gradually developing segments. The segments are from 10 mm. to 12 mm. long, and from 6 to 8 mm. broad. The proglottides differ in this respect from those of the beef tapeworm; the segments nearer the head may be much broader than long. The uterus is broader, coarser.

and the median tube larger, with fewer branches—six to ten, but little over half the number commonly seen in the beef tapeworm. The eggs are about the same size as those of the Tænia saginata, 30 μ to 35 μ, but more spheroid.

The **scolex, larval, juvenile,** or **cysticercus form** of the Tænia solium has long been known, but Küchenmeister, by feeding experiments, demonstrated that the so-called **cysticercus cellulosæ** is but the larval form of the Tænia solium. The larvæ are most frequently developed in the hog, gaining ingress as already described when considering the similar stage in the beef tapeworm. The habits of the hog, however, render measles much more common in that animal than in the ox. Either by the accidental contamination of the hands, and subsequent ingestion of the ova, or possibly by regurgitation during vomiting, occasionally the ova reach the human stomach; as in the beef larvæ in the ox, the liberated larvæ of the solium in man may become widely disseminated. **Cysticercosis,** most common in the insane, is usually the result of coprophagy. When the parasite lodges, a cyst follows, and whether in man or the hog, a

FIG. 106.—HEAD OF TÆNIA SOLIUM. ON THE RIGHT EGG OF TÆNIA SOLIUM.—(*Gould.*)

FIG. 107.—CYSTICERCUS CELLULOSÆ. COMPLETION OF HEAD FORMATION. — (*After Leuckart.—Coplin and Bevan.*) × 12 diameters.

"measle" results. The cyst formed is much larger, as a rule, than in the ox, and may attain the size of 20 mm., the beef measle rarely exceeding 7 mm. While the beef measle is rarely, if ever, seen in man, this form is not infrequent. The method of invasion is probably the same from both cysticerci; both the embryos, when liberated in the stomach, have six hooklets, arranged in pairs, by which they tear and propel their passage through the wall of the viscus.

There are a number of tapeworms of the genus Hymenolepis[1] occurring in man. The most important of these is the **Hymenolepis nana,** also called the *Tænia nana*. The parasite is 5 mm. to 35 mm. long, and 0.5 mm. to 0.9 mm. in breadth. The head is round, 215 μ to 480 μ in diameter; it possesses four suckers and a retractile rostellum armed with twenty-four to twenty-eight hooklets arranged in a single row. The hooklets vary in length from 4 μ to 18 μ. The length of the proglottides is much less than their breadth; the genital pores open on the left side near the anterior border of the proglottis. The fully formed segments

[1] Ransom, Bulletin No. 18, of the Hygienic Laboratory, 1904, gives a detailed description of these parasites.

are distended with eggs; a single proglottis may contain as many as 100 ova. The size of the egg varies materially; Ransom gives from 36 μ by 32 μ, to 56 μ by 42 μ. Infection by the parasite is not common; Ransom has been able to collect 106 cases. Most of the patients are males, and usually children. Another parasite belonging to the same genus is the **Hymenolepis diminuta** (*Tænia flavopunctata*); the length of the strobile rarely exceeds 60 mm., the width 2.5 mm. by 4 mm. The globular head measures 200 μ to 600 μ, possesses suckers and rudimentary unarmed rostellum; the eggs are round or slightly oval, 64 μ to 80 μ in diameter. The parasite is also found in rats. The larvæ are developed in meal moths and beetles.

Tænia Echinococcus[1] or **Dog Tapeworm.**—The sexually mature worm inhabits the intestine of the dog and wolf. It is an insignificant parasite in appearance when compared with the larger forms, rarely attaining a length of five millimeters. When fully developed, there are five segments; the anterior is slender and is continuous with the head; the fol-

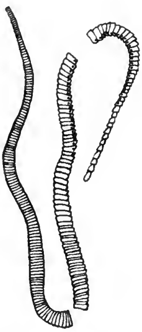


FIG. 108.—HYMENOLEPIS DIMINUTA.

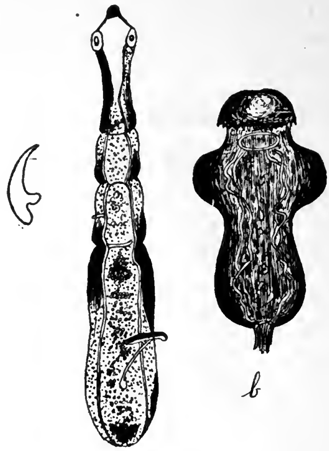


FIG. 109.—TÆNIA ECHINOCOCCUS.—(*After Leuckart—Coplin and Bevan.*)

a. Adult parasite. *b*. Head of echinococcus veterinorum. On the left, a detached hooklet, as seen in fluid from cyst.

lowing segment is the shortest, and the posterior, the longest. Often more than half of the length of the parasite is in the last segment; from time to time the large link is thrown off, so that is is not uncommon to find but the three proglottides. The worm is short lived, and is probably the least prolific of the cestodes; this is compensated for by the proliferative power of the parasite in the juvenile or larval stage. The anterior segment, or scolex, is surmounted by four suctorial discs, anterior to which, between the quadrately placed sucking discs, is the rostellum, with its hooklets, numbering from thirty to forty. The adult worm is not found in man. The ova thrown off by the parasite, entering the alimentary canal of man and some lower animals, hatch the embryo, which, wander-

[1] Lyon, "Virginia Med. Semi-Monthly," Jan. 10, 1902. Melnikow-Raswedenkow, "Zeigler's Beitr.," 1901, Bd. iv, Suppl. MacPhatter, "St. Louis Med. Review," Jan. 28, 1905. Beha, Inaug. Diss. Freiberg, 1904. Dévé, "C. R. Soc. de Biol.," Tome v, 1903, p. 1369.

ing into the tissues of some organ, develops into a cyst—the encysted parasite. These cysts occur in three forms:

1. **Echinococcus scolicipariens, echinococcus granulosus,** or **echinococcus veterinorum,** is a bladder-like cyst, varying in size, often 5 cm. to 15 cm., or even 20 cm., in diameter. The wall of the cyst is formed of two layers, as a rule, easily distinguished from adjacent structures and from each other. The outer layer is supplied by the invaded organ, and is called the cuticular membrane, the tissue of which shows distinct lamination; the inner layer, which is finely granular, constitutes the granular or parenchyma layer. When the cyst has attained a diameter of 2 cm. to 10 cm., the development of brood capsules begins. These will be found attached to the granular layer, first as dot-like bodies, later as distinct cysts, in which many young parasites occur; hence they are spoken of as brood cysts. The heads or scolices, projecting

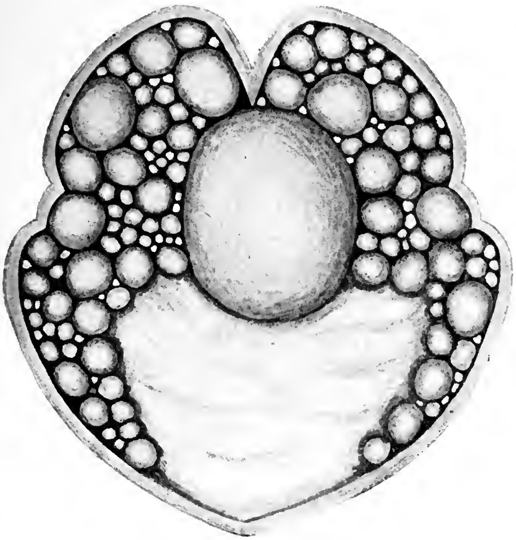


FIG. 110.—HYDATID CYST, SHOWING DAUGHTER CYSTS.

In the lower part of the figure is a whitish mass containing parts of the walls of ruptured daughter cysts. The thick wall of the mother cyst is well shown. (Removed by Dr. H. R. Loux from the liver of a man aged twenty-seven years. The illustration is two-thirds the natural size. Weight, 197 gm. The patient recovered.)

into the cyst, are about 0.3 mm. long, have developed four suckers, and a rostellum with attached hooklets; the interior shows a vascular system and sometimes granular, chalk-like bodies within; at times a parasite may be found with the scolex invaginated into the posterior part of the body, as though retracted.

2. **Echinococcus hydatidosus, Echinococcus altriciparieus,** or **Echinococcus hominis,** is characterized by the development of daughter cysts, probably from degeneration of the brood capsules already described. From the daughter cysts another generation of parasites may develop, forming still another series of cysts. The number of daughter cysts may be enormous: as given by Thoma, 1000.

3. **Echinococcus multilocularis** bears little resemblance to the forms

just mentioned; the cysts never attain any great size, but occur in enormous numbers. The liver is the common site of this form, which is very rare in the other organs. Earlier observers regarded the growth as an alveolar, colloid tumor. The cysts rarely attain a diameter of over one centimeter, are spheric or ovoid, the wall formed by a dense connective-tissue membrane, which, under the microscope, may contain still smaller alveoli; the alveoli are filled with a more or less gelatinoid or colloid material containing a few of the histologic elements of the scolex. Often only on prolonged examination can these be demonstrated. The cysts may communicate with one another. From careful recent studies Melnikow-Raswedenkow, Dévé and others are convinced that multilocular echinococcal disease is due to a special parasite. The geographic distribution of the two forms is not the same; there are areas in Europe in which the multilocular form is common and the classic echinococcus is almost unknown.

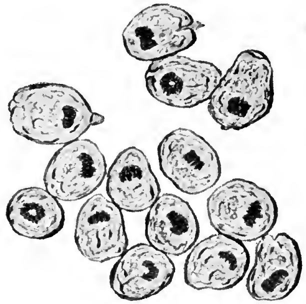


FIG. 111.—ECHINOCOCCUS. A GROUP OF SCOLICES.—(*From Dr. Loux's case*, see Fig. 110. 1/2-in. obj.: 1-in. oc.)

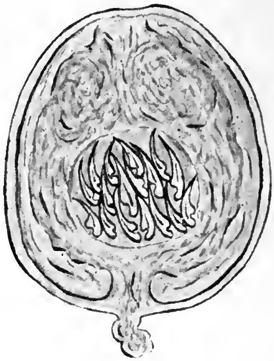


FIG. 112.—ECHINOCOCCUS.
Scolex: *a*, pedicle of attachment to endocyst. Just above are shown the somewhat disarranged hooklets.—(*From Dr. Loux's case*, see Fig. 110. 1/4-in. obj.; 1/2-in. oc.)

Echinococcal cysts may occur in almost any part of the body. In over fifty per cent. of the cases the liver is affected. The lungs are involved in about ten per cent., kidneys ten per cent., the muscles, subcutaneous tissues, and bones, ten per cent., central nervous system five per cent., and the remainder distributed in the sexual organs, spleen, heart, eye and orbit; of the latter about fifty cases are on record. Marshall could find but three cases in which the eyeball was involved. Occasionally the cysts are in the myocardium, and there are recorded instances in which a cyst loose in the circulation caused death by occluding the pulmonary artery.[1]

Demonstration.—The diagnosis of echinococcus-cyst is commonly based upon finding the hooklets or scolices. The presence of a fluid with a comparatively low specific gravity, and nonalbuminous or containing but a minute trace of albumin, should always be looked upon as indicating an echinococcus collection. When the fluid is clear and contains but a small quantity of suspended material, sedimentation

[1] Quill, "Jour. of Royal Army Med. Corps," April, 1904.

should be permitted to take place, and the sediment may be further brought together by the centrifuge, if necessary. A small quantity of the sediment is placed on a slide in the same manner as directed for urine; examination made by the $\frac{1}{4}$-inch objective will usually show the hooklets quite plainly. Occasionally, coccidial cysts, and possibly cysts arising from other causes, contain sickle-shaped bodies, which may mislead the inexperienced. The hooklets of the echinococcus have on the concave side a knob, or protuberance, or hump, the appearance of which is not fully reproduced by anything with which the author is familiar. The brood capsules and contained scolices can rarely be demonstrated in the fluid drawn from such cysts by tapping. If, however, the cyst wall be accessible, gentle scraping will usually detach the capsules, some of which may escape rupturing. These are best shown on the slide under comparatively low magnification—1-inch or $\frac{1}{2}$-inch objective. (See Figs. 111 and 112).

FIG. 113.—ECHINOCOCCUS-HOOKLETS.—(*From Dr. Loux's case*, see Fig. 110. $\frac{1}{4}$-in. obj.; 1-in. oc.)

Occasionally, the cyst may be inspissated as a result of the death of the contained parasites. Under such circumstances the contents may be cheesy, resembling the caseous collections of tuberculosis and syphilis. The demonstration of the hooklets in this material becomes somewhat more difficult. A considerable quantity of the suspected material should be washed in alcohol, the alcohol drained off, and the washing repeated; this may be followed by washing in ether to complete the removal of any fat, and, finally, the remaining sediment may be transferred to the slide and examined as already directed. If these directions are carefully followed, the hooklets can usually be found; sometimes, however, prolonged search will be necessary.

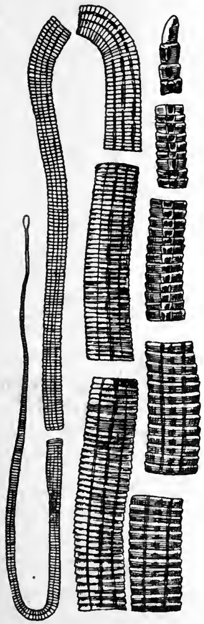


FIG. 114.—DIBOTHRIOCEPHALUS LATUS.—(*After Leuckart.—Gould.*)

FIG. 115. — FREE-SWIMMING EMBRYO OF THE DIBOTHRIOCEPHALUS LATUS. — (*After Leuckart.—Gould.*)

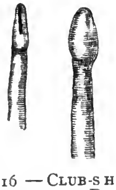


FIG. 116 —CLUB-SHAPED HEAD OF THE DIBOTHRIOCEPHALUS LATUS.—(*After Leuckart.—Gould.*) A. Seen from the edge. B. Seen from flat surface.

The **Dibothriocephalus latus**[1] (*Tænia lata*, *Bothriocephalus latus*, broad tapeworm) is the largest cestode, often attaining a length of five to ten meters and comprising 2000 to 4000 proglottides.

[1] Fleckseder and Stejskal, "Wien. klin. Woch.," July 14, 1904, p. 793. Edsall, "Amer. Med.," Dec. 24, 1904, p. 1087.

Usually but one parasite is present, although Zinn reported a case in which there were seven.

The head is clavate, rather elongated, has a long elliptic sucker on each side, measures about 1.5 mm. long by 1 mm. wide, and is without either rostellum or hooklets. The fully developed joints are from two to four times as broad as long; the breadth of the link may reach 1.8 cm. The genital aperture is always on the ventral aspect, and is central. The eggs are brownish, oval, 60 μ to 70 μ in length, 40 μ to 45 μ broad, and the shell is furnished with a lid or operculum, through which, after some months in water, the embryo escapes. Braun has observed scolices, believed to be of the dibothriocephalus, in pike and trout, and by feeding the fish to dogs has led to the development of the tapeworm in the dog. The fully grown worm is said to be the longest of tapeworms.

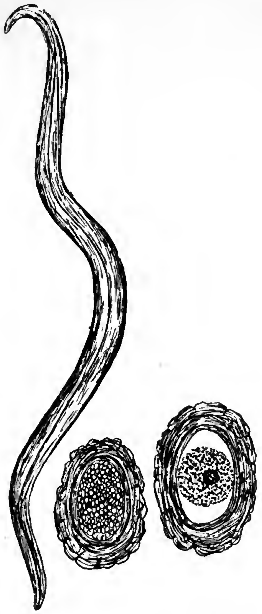


FIG. 117.—ASCARIS LUMBRICOIDES AND EGGS.—(*Coplin and Bevan.*)

Of the 22 cases reported in this country all of the patients were foreign born. The presence of the parasite in the intestine is frequently, although not constantly, accompanied by an intense anemia resembling pernicious anemia and, if untreated, is frequently fatal. The recognition of dibothriocephalus infection depends upon the demonstration of segments, or ova, in the feces. The almost square proglottides, with the genital openings centrally located, and the simple convoluted uterus containing the eggs, render the diagnosis not difficult. The slightly elongated ovum with the operculum or lid situated at one end usually permits a ready diagnosis.

The **nematodes** occurring in man are cylindrical worms usually tapering at both ends. They are not hermaphroditic and the females are generally larger than the males. For complete development some of the nematodes require two hosts; others may pass from egg to adult worm in a single individual.

The **Ascaris lumbricoides**[1] is a yellowish or yellowish-brown worm, varying in length; the female measures about 15 cm. to 30 cm.; the male, 9 cm. to 20 cm. The worm is striated transversely and possesses four longitudinal bands. Round worms are most common in children, occupying the upper portion of the small intestine, from which they may wander into the bile-ducts, stomach, esophagus, nose, Eustachian tube, and larynx. The number in any case varies; rarely are they present in large numbers. The ova are ellipsoid, 50 μ to 70 μ in their longest diameter and 35 μ to 50 μ in width; each egg possesses a dense enveloping membrane.

Collected in masses ascarides may give rise to intestinal obstruction.

[1] See Braun, foot-note, p. 181. Vaullegeard, "Bull. Soc. Linn. Normandie," 5e Ser., 1901. Wagner, "Deut. med. Woch.," vol. xxviii. Pierantoni, "Gazz. Osped.," May 31, 1903. Stott, "Northwest Medicine," Oct., 1903, p. 532. Ager, "Amer. Med.," June 21, 1902, p. 1062. Negresco, "Soc. de Med. Legale," Nov 9, 1903.

Ordinarily the worm does not migrate into the stomach, but occasionally it does so and is vomited. In typhoid and scarlet fevers, or other conditions in which the patient is greatly weakened or unconscious, the parasites may collect in numbers in the esophagus and cause collapse of the larynx by pressure; in other instances they wander into the larynx and may occlude the chink, giving rise to fatal asphyxia. The profession is not agreed as to the possibility of lumbricoides penetrating or perforating the intestinal wall. Usually when the parasites are found in the peritoneal cavity they have escaped through perforations due to other causes. Evans states that in the pig they are frequently found attached to the mucosa, and numerous cases have been reported in man where it was believed that the worm had perforated the gut. It has usually been held that ascarides produce no poison. Pierantoni has shown that lumbricoides yield toxic substances which produce mydriasis, and is of the opinion that the nervous symptoms sometimes seen in these cases may be due to toxic substances derived from the parasite.

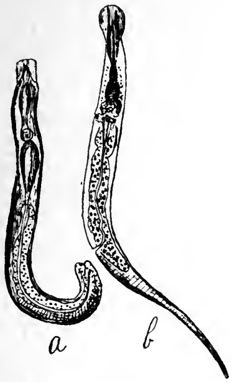


FIG. 118.—OXYURIS VERMICULARIS.—(*Coplin and Bevan.*)

a. Female. *b.* Male.

FIG. 119.—MALE TRICHOCEPHALUS, TRICHIURUS, OR WHIPWORM.

A large part of the cephalic end of the worm has transfixed a fold of the intestinal mucosa.—(*Cohen.*)

The **Oxyuris vermicularis** (*thread-worm* or *pin-worm*) inhabits the colon and rectum, occasionally, in the female, involving the rectum and vagina. The female parasite is 8 mm. to 12 mm., and the male 3 mm. to 6 mm. in length. The oval egg is 30 μ to 50 μ long, 20 μ to 30 μ wide, and possesses a thin shell which offers some protection to the contained embryo when subjected to the influence of drying. The parasite wanders from the anus and provokes violent itching, which not uncommonly causes the patient to lacerate the skin by scratching; this in turn is followed by infection, giving rise to refractory inflammation or even ulceration. As no intermediate host is necessary, the patient may be reinfected by ova carried to the mouth on the hands soiled by scratching. From the time the ova enter the mouth about two weeks are necessary for the adult worm to appear in the feces. The worm has been found in the appendix either singly or in masses, and it is not impossible that it may cause appendicitis.

The round worm usually known as the **Trichocephalus dispar** (whip-

worm) is properly called the **Trichocephalus trichiurus.** The anterior two-thirds of the parasite is thread-like or filamentary; the remainder is conic, and in the male is coiled like a spring. The female is 4 cm. to 5 cm. long, the male somewhat shorter. The oval eggs are 50 μ long and 20 μ in diameter, yellowish brown, and at each end possess a knob-like protuberance. The parasite inhabits the colon, particularly the cecum, and may invade the small intestine and the vermiform appendix. Girard[1] has shown that the cephalic end of the parasite may be imbedded in the mucosa of the appendix. Askanazy has found that the Trichocephalus abstracts blood; Becker[2] and others have reported cases of severe anemia showing no improvement until, by appropriate treatment, the parasites have been removed.

Strongyloides intestinalis[3] (*Anguillula intestinalis*, or *Anguillula stercoralis*) is found in the upper part of the small intestine; rarely the adult worm may be present in the feces. The female is 1.5 mm. to 2 mm. long, 0.05 mm. to 0.07 mm. broad. The male has not been identified, and it has been suggested that the eggs are parthenogenetic, giving rise to both male and female embryos. The body tapers anteriorly and posteriorly terminates bluntly. The eggs can be seen in the interior of the parasite, sometimes containing embryos; when hatched, the embryo is slender, actively motile, rarely measuring 0.5 mm. The parasite is frequently present in diarrhea, of which it is said to be a cause.

Trichiniasis[4] is a disease affecting man and due to the *Trichina spiralis*, or more correctly **Trichinella spiralis.** The life of the parasite may be divided into three stages: the embryo, the encysted larva, and the adult worm. According to Stiles, the encapsulated larvæ have been found in about twenty-five different mammals, including man; it is most common in the hog; infestation in man is usually due to the consumption of trichinous pork.

In the muscle the parasite, in the form of its embryo, will be seen as a coiled-up worm 0.05 mm. in length, surrounded by a capsule that at first is translucent, later becoming opaque, and eventually calcareous. If meat containing the embryo be eaten, the capsule is digested in the stomach, the embryo liberated, and its final development into the adult worm completed in the small intestine. The fully grown female trichinella measures 3 mm. to 5 mm., the male about half as much. The adult parasite inhabits the duodenum and jejunum, in which she liberates the embryos. It is not certain whether the latter are thrown off in the intestinal cavity, from which they penetrate the wall of the gut, or the adult female enters the intestinal wall and discharges the embryos in the lymph or blood-vessels. The dissemination of the embryo is evidently accomplished through the blood and lymph streams.

Although not infrequently found in other tissues, the destination of

[1] "Annales de l'Inst. Pasteur," 1901, t. xv.

[2] "Deut. med. Woch.," June 26, 1902.

[3] "Jour. of Exper. Med.," 1901–05, vol. vi, p. 75. Exhaustive discussion of the parasite with full bibliography, by Thayer. See also Wainwright and Nichols, "Med. News," 1904, p. 785.

[4] Stiles, "Trichinosis in Germany," Bulletin No. 30, U. S. Dept. of Agriculture, 1901. Ossipow, "Ziegler's Beitr.," 1903, Bd. xxxiv, Heft 2, p. 253. Schleif, "Deut. Arch. f. klin. Med.," Bd. lxxx, p. 1. Gould, "Amer. Med.," Sept. 26, 1903, p. 575. Opie, "Amer. Jour. of the Med. Sci.," March, 1904. Williams, "Jour. Med. Research," July, 1901.

the worm seems to be in the muscles; here it coils up, and is surrounded by a capsule partly produced by the reaction of the surrounding tissue. The changes that this capsule undergoes have already been noted. It is estimated that from 1000 to 2000 embryos may be hatched by a single female trichinella. The dissemination of these, by the route previously indicated, may be associated with fever, muscular pains, more or less edema, and even paralysis. A small percentage of the cases terminates fatally. A recent and important contribution to the diagnosis of trichiniasis is the discovery of the enormous increase of the eosinophile cells in the blood. The lesion in the muscle is essentially a parasitic myositis through the activity of which the encapsulating fibrous tissue is produced.

Demonstration.—This may be accomplished by teasing the suspected muscle as follows: Clean a slide thoroughly and breathe upon its surface, thereby slightly moistening it; upon the moistened surface lay a fragment of the muscle to be examined; with needles tear the fragment to pieces;[1] add a drop of glycerin and a cover-glass; examine with a $\frac{1}{2}$-inch or $\frac{1}{4}$-inch objective. In order to make the specimen permanent, wash out the glycerin with water, dehydrate with alcohol,

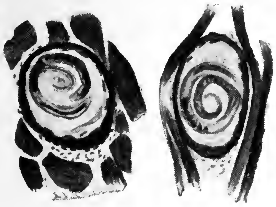


FIG. 120.—TRICHINELLAS IN THE GASTROCNEMIUS MUSCLE OF MAN; OBLIQUE SECTION. Two fairly well preserved parasites and capsules.

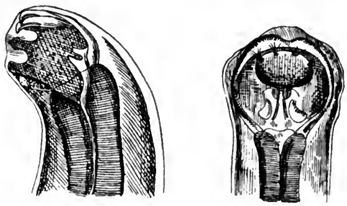


FIG. 121.—CEPHALIC EXTREMITY OF UNCINARIA DUODENALIS ("OLD-WORLD HOOK-WORM") PROFILE AND FRONT VIEW.—(*After Leuckart.—Gould.*

clear in creasote or oil of cloves, apply balsam, and cover. The fragment of muscle may be obtained by incision, using cocain as a local anesthetic, or it may be removed by a punch or harpoon.

Uncinariasis,[2] also called *ankylostomiasis*, results from the presence in the intestine of a hook-worm of the genus Uncinaria, family Strongylida. Two species, the **Uncinaria duodenale** and the **Uncinaria americana,** occur in man. The American parasite differs from the old-world hook-worm in the character of its oral armature and the size of the ova. The Uncinaria duodenalis is identified by the fact that the mouth possesses two pairs of hook-like ventral teeth and one pair of dorsal teeth. The ova measure 50 μ to 60 μ by 32 μ. In the new-world parasite the two pairs of ventral hooklets are replaced by semilunar plates or lips and one pair of similar dorsal structures; there are also a dorsal, conic, median tooth which projects into the buccal cavity, and deep

[1] This procedure is technically known as "teasing" the specimen.

[2] The literature of this subject may be followed from the Report of the Commission for the Study and Treatment of Anemia in Porto Rico, San Juan, Dec. 1, 1904. See also Harris, "Amer. Med.," July 19, 1902, p. 99. Capps, "Jour. Amer. Med. Assoc.," Jan. 3, 1903, p. 28. Baker, "Brit. Med. Jour.," March 28, 1903, p. 718. Allen J. Smith, "Amer. Jour. Med. Sci.," 1903, vol. cxxvi, p. 768.

in the capsule one pair of dorsal and one pair of ventral submedian lancets.[1] The ova measure 64 μ to 76 μ by 36 μ to 40 μ.

The female uncinaria measures 9 mm. to 16 mm., and the male 7 mm. to 9 mm. The head of the parasite is bent backward, giving the cephalic end the contour of a hook, from which it receives its name. The posterior end of the female is conic, that of the male flaring or umbrella-like, and from the center projects the sheath containing the penis. The eggs when passed may show segmentation or contain a developing embryo which often can be seen moving inside the shell. The further development of the parasite is accomplished in moist earth, in which, after a number of ecdyses, it becomes encysted and ready to infect man.

FIG. 122.—DUODENUM SHOWING ATTACHED UNCINARIÆ. A, A. Papilla-like elevations with central depressions resulting from detachment of parasites. (Specimen presented to the Museum of the Jefferson Medical College by Capt. C. F. Kieffer, U. S. A.)

The belief, at one time prevailing, that infection occurred almost exclusively through water, has been largely abandoned. The observations of Looss, corroborated by Claude A. Smith and others, have clearly established that the parasite enters through the skin. There is no doubt that a papular, vesicular, or pustular lesion (ground itch) may occur at the point of inoculation, although this frequently escapes observation; it is probable that the parasite passes by the circulation to the lung, where, on account of its size, the capillaries are ruptured, and with the sputum the worm is swallowed, finally developing in the duodenum. The transcutaneous infection is not the only way by which the parasite may reach the intestine. Dirt-eaters may introduce the parasite in a form adapted to its further development in the alimentary canal. The point of attachment corresponds to the area of maximum alkalinity of the bowel contents, extending from the second portion of the duodenum to the upper end of the ileum. The number of parasites present may be enormous; Ernst found 2768 in the intestine of a brick-maker. Sometimes the worm is half buried in the intestinal mucosa. The number found attached at autopsy is usually not large. Often small elevations with blood-marked punctures in the center indicate the points from which the parasites have become loosened.

The lesions produced by the uncinaria may be brought about partly

[1] Report of the Commission for the Study and Treatment of Anemia in Porto Rico, San Juan, Dec. 1, 1904, p. 29.

by the loss of blood induced through the wounding of the duodenum, partly by the associated inflammatory processes, which may not be marked, and possibly, to a certain extent, by the absorption of metabolic products elaborated by the parasite. Allen J. Smith and Loeb have shown that the uncinaria of the dog produces a hemolytic poison, and it is probable that some similar toxic substance is elaborated by the hook-worms in man. Ordinarily the amount of blood extracted can not be large, although no doubt the continued loss of a small quantity must exert considerable influence on the blood-making tissue. That more blood is lost than is actually drawn by the parasite is shown by the occasional presence of submucous hemorrhages at points where the parasites have been attached; occasionally these small blood-cysts contain a hook-worm. More or less fatty degeneration occurs in the heart, liver, and kidneys; the periphery of the liver lobules not uncommonly contains an orange-yellow pigment, and there may be areas of necrosis surrounding the intralobular vein. The presence of fat and pigment and the occurrence of necrosis strongly indicate the action of some toxic substance. The hemoglobin is low (about forty per cent.) and the erythrocytes reduced to 2,500,000, although counts of less than 1,000,000 have frequently been observed. Poikilocytosis, polychromatophilia, and nucleated red cells occur in marked cases. Eosinophilia is the most prominent feature, and over two-thirds of the leukocytes may be of this type. Sometimes the lymphocytes are increased and peculiar myelocytes are occasionally observed. The polymorphonuclear cells are as markedly reduced as the number of eosinophiles is increased; otherwise the percentage is not materially altered.

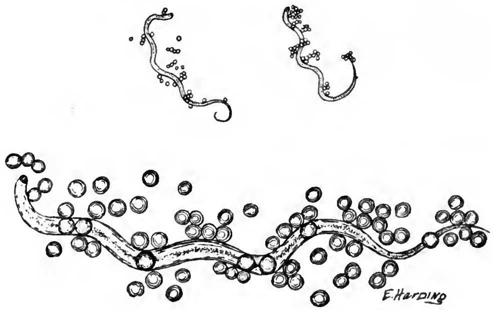


Fig. 123.—Filaria Embryo.—(*From F. P. Henry's case.*) The two embryos shown above were drawn from ⅔-inch objective; the lower from ¼-inch objective. Red blood-cells are introduced for comparison.

Filariasis should properly include all the morbid conditions due to filaria, but, apparently by general consent I believe, the name is largely, if not exclusively, restricted to manifestations associated with the presence of filaria embryos in the blood. **Filariosis,** better than filariasis, conforms to the names given other parasitic affections, and probably will supplant the latter term. Two filarial diseases will be considered,—one manifested by the presence of embryos in the circulating blood, and the other in which the only manifestation is a local one due to a peculiarity in the method by which the parent worm extrudes her embryos.

The term **Filaria sanguinis hominis**[1] is applied to filaria embryos that are found in the circulating blood. The parasite, as seen in

[1] Important literature on filariasis is given by DaCosta, "Clinical Hematology," second edition, 1905, pp. 413 to 421.

the blood, is an actively motile, cylindric body, about the diameter of an erythrocyte, 0.2 mm. to 0.3 mm. long, somewhat blunted anteriorly and sharp or truncated at the tail end. In some of the embryos there is a refractile V-shaped spot near the cephalic extremity. Manson suggests that this is a rudimentary water vascular system. An important differentiation between the filaria is the now thoroughly established fact that in certain types of the affection the embryos are found in the peripheral blood during the day-time only (*Filaria sanguinis hominis diurna*), others are found at night (*Filaria sanguinis hominis nocturna*) and not in the day-time, and in another group they are constantly present in the peripheral blood (*Filaria sanguinis hominis perstans*). The following table by Prout[1] shows the resemblances and important differences between the three filariæ mentioned:

TABLE SHOWING IMPORTANT CHARACTERS OF THREE EMBRYO FILARIÆ.

	F. DIURNA.	F. NOCTURNA.	F. PERSTANS.
Length,	0.3 mm.	0.3 mm.	0.23 mm.
Breadth,	0.0075 mm.	0.0075 mm.	0.00455 mm.
Sheath,	Present.	Present.	Absent.
Head,	(?)	Cephalic armature, six-lipped.	Papillated.
Tail,	Sharp.	Sharp.	Truncated.
Body,	Central granular aggregation.	Ill-defined aggregation.	No central aggregation.
V spot,	Present.	Present.	Absent.

More is known of the filaria nocturna than of other members of the group. While, as its name indicates, it is found in the peripheral blood in the night-time only, if the host changes his habits and is active during the night, sleeping in the day-time, the period of peripheral appearance of the parasite is also perturbed and may be reversed. The embryo is transferred from man to man by the mosquito (Culex fatigans and certain Anopheles), in which it undergoes important developmental changes. In the stomach of the mosquito the filaria sheds its sheath, penetrates the intestinal wall, enlarges and undergoes a further metamorphosis, finally reaching the labium and proboscis, from which it enters the blood of the next individual bitten.

In order to demonstrate the embryos in the blood it is necessary to make the examination at a time corresponding to the habits of the particular filaria sought. A fairly large drop of the freshly drawn blood is placed on the slide and a cover-glass at once applied. The actively motile embryo is readily recognizable, even with low powers, and usually is observed lashing about among the cells, coiling and uncoiling and sometimes progressing in an aimless sort of way. After a few hours, and especially when cooled, the movements become less rapid, eventually sluggish, and finally cease. Permanent mounts may be prepared from dry films, fixed for fifteen minutes in a mixture composed of equal parts of absolute alcohol and ether; after fixation the spread is air-dried and

[1] "Brit. Med. Jour.," Jan. 26, 1901, p. 210. I have omitted the column describing the organism of which Prout writes.

stained for five minutes in a one per cent. aqueous solution of thionin; wash in water, dry, and mount in balsam. The stains devised by Leishman, Jenner, and Wright[1] may be used, but give less satisfactory results.

The adult parasite producing the embryo of the Filaria sanguinis hominis nocturna is called the *Filaria bancrofti*, and inhabits the lymphatics of the trunk—particularly of the abdomen—and occasionally the extremities. Sometimes a number (six or seven) of the adult worms occur together. The parasite may be in the lymphatics of the scrotum, inguinal region, or retroperitoneal lymph-vessels. Although the embryos circulating in the blood—estimated by Manson to number 40,000,000 or 50,000,000—give rise to no important pathologic process, there are a number of more or less grave conditions resulting from the lymph stasis and inflammatory phenomena induced by the presence of the parent worm in the lymph-vessels. The Filaria bancrofti is a

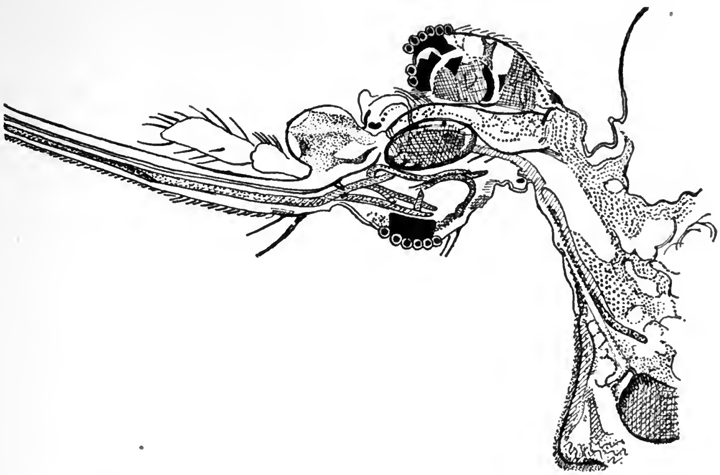


FIG. 124.—SECTION OF HEAD OF MOSQUITO SHOWING FILARIA IN POSITION TO BE INOCULATED DURING THE ACT OF BITING.—(*From Howard, after Manson.*)

hair-like parasite 1 mm. to 2 mm. in diameter and sometimes attaining 1 meter in length. As is usual with parasites, the male is the smaller. The lesions produced by the adult worm are grouped under the names elephantiasis and elephantoid disease.

Elephantiasis usually affects either the lower extremities or the scrotum. It is commonly preceded by lymphangitis, which is followed by a gradually evolved, but eventually enormous, hyperplasia of the connective tissues. Manson believes that the extensive lymphatic obstruction and connective-tissue overgrowth are due to the premature escape of ova into the lymph-spaces. The extent of the connective-tissue hyperplasia may be indicated by the fact that the scrotum may attain a weight of 200 pounds, and the leg at the calf may measure 24 to 30 inches in circumference.

[1] See Chapter I, Part III; Technic of Blood Examination.

Manson considers chyluria, varicose inguinal glands, lymph scrotum, and chylocele as **elephantoid diseases.** The first of these (**chyluria**) is characterized by a milky white or pinkish urine which may contain coagula or undergo spontaneous coagulation, so that if the urine be passed into a glass, the latter may be inverted without spilling the contents. In some cases the urine also contains blood—**hematochyluria. Varicose inguinal glands** are manifested by a lobulated enlargement near the base of Scarpa's triangle. In **lymph scrotum** a milky or pinkish fluid collects in the connective tissues or in the manifestly varicose lymphatics of the organ. In **chylocele** the tunica vaginalis contains lymphous fluid, milky or reddish in color. In the chylous urine and lymph obtained by pricking the tissues or tapping the lymph-

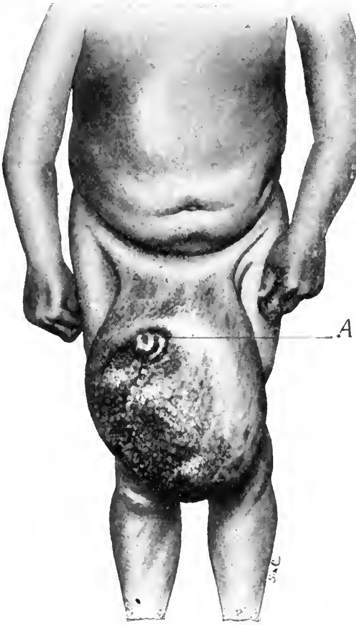


FIG. 125.—ELEPHANTIASIS OF THE SCROTUM.
The mass weighed nearly 15 kilos (31 pounds). *A*. Penis.

vessels not infrequently filaria embryos or eggs are found. Pyogenic infection may give rise to suppurative processes in the lymph scrotum, in varicose lymph-nodes, and, though less commonly, in the hyperplastic connective tissues of filarial elephantiasis.

Dracontiasis[1] or **guinea-worm disease** is an affection due to the **Filaria medinensis** (*Dracunculus medinensis*, *guinea-worm*), of which the female only is known. Powell has demonstrated that the period between

[1] Francis, "Amer. Med.," Oct. 26, 1901. Powell, "Brit. Med. Jour.," Jan. 9, 1904, p. 73. Beclere, "Soc. med. des Hôp.," July 17, 1903. Powell, "Trans. of the Bombay Med. and Physical Soc.," Sept., 1903. Remlinger, "C. R. Soc. de Biol.," 1904, vol. lvii, p. 76.

infection and the appearance of the worm is about one year. The female is about 60 cm. to 90 cm. in length and 2 mm. in diameter, and is commonly solitary, although not always so. It is usually claimed that the parasites—probably both male and female—enter with the food; only the female develops. It penetrates the mucosa and eventually reaches the subcutaneous tissues, in which it completes its development. Harrington does not believe in the entrance of the parasite through the alimentary canal. He is of the opinion that it is introduced either in some embryonic form, as by the mosquito, or that in some other way it gains access to the subcutaneous tissues directly from without. In no other way is it possible to explain the fact that over seventy-five per cent. of the lesions occur in the lower extremities, and the greater

FIG. 126.—DRACONTIASIS, OR GUINEA-WORM DISEASE.

A case of Filaria medinensis (reported in "American Medicine," October 26, 1901, by Dr. Edward Francis) The abscesses and swelling of both feet are well shown. From the left foot three protruding worms can be seen; this limb is the more swollen. But one worm can be seen protruding from the right foot There were five worms in this case; four are shown. The patient recovered.

number below the knee. During the period in which the parasite is developing in the subcutaneous tissues it may be distinctly palpable; finally suppuration ensues and the worm is cast off, with innumerable ova; the latter, when thrown into water, penetrate the cyclops, in which further development occurs. The parasite has been observed in a patient, a native, and always a resident, of Philadelphia, but it is rare in this country.

In filariasis due to the Filaria sanguinis hominis a moderate increase in the eosinophiles is not uncommon. In dracontiasis thirty to forty per cent. of the leukocytes may be eosinophiles.

Among the other filaria occasionally observed in man are: Filaria

bronchialis, found in the bronchi; Filaria loa (3 cm.), found in the conjunctiva; Filaria hominis oris, in the mouth, etc.

The most important of the **Arthropodæ** affecting man are the mites or ticks belonging to the Acaridæ. The diseases produced by the mites are called **Acarinoses.**

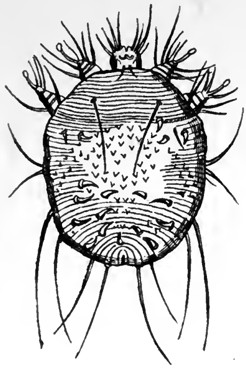


FIG. 127.—ACARUS SCABIEI.

Scabies or *itch* is due to the **Acarus scabiei** (*Sarcoptes hominis* or *itch-mite*). The female is nearly double the size of the male, and can often be picked out of the furrows found in the skin in cases of itch. The parasite is from 0.2 mm. to 0.5 mm. in length, and over one-half as broad. It possesses four pairs of legs, two pairs anteriorly and two posteriorly. From each of the foremost pair of the anterior legs, extend delicate processes, supplied at the distal end with discoid terminations for attaching themselves to surfaces; in the male these addenda are on the hindermost pair. The other legs end in bristles. The posterior border is marginated by a number of bristle-like hairs; similar hairs are seen on the rounded head of the mite.

The parasite burrows into the epidermis, in which it forms cavernous systems attended with inflammation of the adjacent Malpighian layer. In the cuticular caverns the female deposits her eggs, which hatch into young mites. These burrow, shed their external coatings, and repeat the process of reproduction of kind.

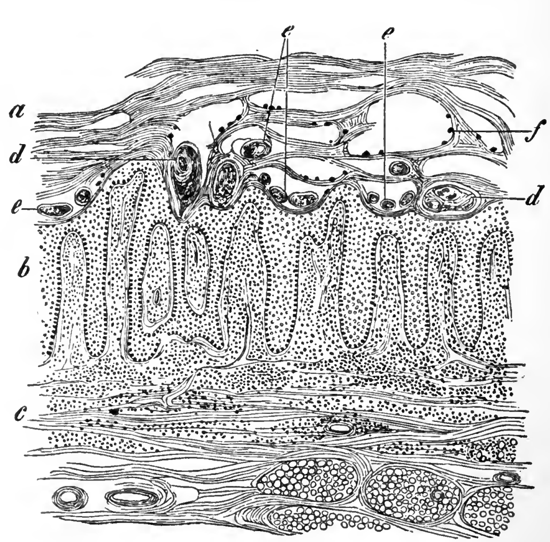


FIG. 128.—SCABIES.
Section of skin showing burrows in the upper layer of the epidermis (*a*), containing female itch mite (*d*), ova (*e*), and excreta of the parasite lying in the burrow (*f*). *a*. Horny layer. *b*. Malpighian layer. *c*. Infiltrated cutis.—(*Ziegler*.)

Leptus autumnalis, or *harvest-mite* (larva of trombidæ), is a red-colored parasite deposited upon the skin from grass, bushes, and certain cereals; it induces inflammation by its bite and by boring into the epidermis.

Pentastoma denticulatum is the juvenile form of the Pentastoma tænioides. The mature female is 50 mm. to 125 mm. in length and 6 mm. to 10 mm. broad; the male is much smaller—15 mm. to 25 mm. long and 2 mm. to 5 mm. in breadth. The larva is between 3 mm. and 5 mm. in length, and is from 1 mm. to 2 mm. wide—an egg-shaped

mass occasionally found in the viscera. The mature worm is found in the frontal, nasal, and maxillary sinuses of some of the domestic animals.

The **Demodex,** or **Acarus folliculorum hominis,** inhabits the ducts of sebaceous glands and occasionally the hair-follicles. It is broad just back of the head, from which point it tapers down to a blunt hinder extremity; at the broadest part are four short, thick legs. The length of the acarus varies greatly,—between 0.5 mm. and 1 mm.,—and the parasite is usually about one-tenth as broad at the widest point.

Ixodes ricinus, or *wood-tick,* inhabits decaying wood in dry places (dry rot of timber), from which it attaches itself to dogs, and occasionally to man. The head is black or brownish, and supplied with a boring disc, which penetrates the skin, and through which the parasite sucks blood.

The Insecta.—The important insects attacking man are lice, fleas, mosquitos, and flies.

Pediculus capitis, pediculus ordinarius, *head-louse* or *common louse,* inhabits the hairy scalp. The adult parasite is about 1 mm. to 2 mm. in length, and, pathologically, is an epizoon, securing nourishment by attacks upon the skin. The irritation produced by the bites is sometimes followed by inflammation, which may be eczematous in character. The eggs are oval, with slightly flattened ends, and are attached to the hair by a chitinous cement, which also covers them. An egg hatches out in from seven to ten days.

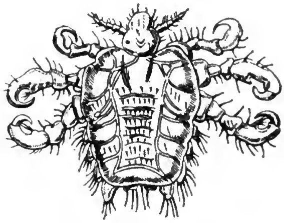


FIG. 129.—PEDICULUS PUBIS.

Pediculus vestimenti, Pediculus corporis humanus, *clothes-louse* or *body-louse,* inhabits the clothing, in which it deposits its eggs. The fully developed parasite is considerably larger than the head-louse. From the clothing the parasite makes incursions to the skin, from which it obtains nourishment. The bites induce changes similar to those of the head-louse.

Pediculus pubis, Pediculus inguinalis, Phthirius pubis or **inguinalis,** or *crab-louse,* infests the hairy pubis, axilla, and, rarely, the beard and eyebrows. The parasite is smaller than either the head-louse or body-louse. Its habits are practically the same as those of the head-louse.

Cimex lectularia, Cimex hirundinis, or *bedbug,* dwells in beds, floors, and cracks of woodwork, from which it invades the skin, the bites producing slight inflammatory lesions. The adult cimex is 3 mm. to 6 mm. in length; the eggs are laid between the months of April and October, and require eleven weeks to hatch and develop the mature parasite.

Pulex irritans, Pulex hominis, or *human flea;* the **Pulex serraticeps, Pulex felis, Pulex canis,** or *dog flea.* The two parasites closely resemble each other, and by some are held to be identical. They infest the hair of the dog and cat, from these animals wandering to man. Closely related to these is the *sand-flea,* **Pulex minimus cutem penetrans,** or **Pulex penetrans,** an exceedingly annoying parasite, smaller than either of the foregoing, and found in the sandy areas of the tropics and subtropics.

Mosquitos or *gnats,* occupying an important position in human pathology, belong to subdivisions of the parasitic genera known as the *Culex,*

Anopheles, and *Stegomyia*. The local lesions induced by the bites of these parasites, while not wholly unimportant, are now considered of more significance than formerly. Their relation to the spread of malaria, filarioses, and other parasitic diseases is discussed elsewhere.

Myiasis[1] is a term applied to pathologic conditions in which the larvæ of flies are found. The human excrement not uncommonly contains larvæ of one kind or another, but it is not known that the parasites provoke any important disturbance. **Maggots,** occasionally seen in dead tissues, and, before the antiseptic methods of to-day, one of the parasites found in wounds, are the larval forms of certain flies. The eggs deposited on the wound surface, dressings, etc., hatch, the resulting juvenile parasites being known as *maggots*. **Screw-worm** disease is an affection seen particularly in the southern and southwestern parts of the United States. The structures involved are the nasal cavity and accessory sinuses. Apparently the parasite never invades a healthy nasal cavity, but is particularly prone to develop in the nose or external auditory canal when chronic inflammatory processes have materially altered the superficial epithelium. From forty to sixty hours after the fly lays the eggs a sanious discharge and often epistaxis appear, followed later by edema of the face and eyelids. The fully formed larva is white, 10 mm. to 12 mm. long, 2 mm. to 3 mm. wide. Robertson[2] reports a case in which there were 120 worms. When unrelieved, the patients frequently die.

Insects and Communicable Diseases.—Recent studies in communicable diseases have shown that certain insects are essential to the propagation of some maladies, and incidentally are of importance in others. In malaria (see p. 188) the mosquito is certainly the most important if not the only means by which the disease is spread; in this affection the sexual cycle of the Plasmodium malariæ occurs in infected mosquitos. Originally suggested by Finlay, and later established by the experiments of Reed, Carroll, and Agramonte, it is generally conceded that the mosquito is necessary to the propagation of yellow fever, the immediate cause of which is not known. In malaria and filariosis the animal parasites undergo definite cycles of evolution in the interior of the insect. In trypanosomiasis the tsetse-fly inoculates the disease from animal to animal, but, so far as at present known, the flagellate parasite has no definite cycle within the insect. In another group of diseases, including cholera, typhoid, tuberculosis, and infections of the types indicated, the germ causing the disease may be deposited upon the food, and in that and similar ways be conveyed from sources of infection to the healthy.[3]

[1] "Exhaustive Contribution to the Study of Insect Fauna in Human Excrement," by Howard, "Proc. of the Washington Acad. of Sciences," Dec. 28, 1900, p. 541.

[2] "Laryngoscope," March, 1898.

[3] Engelmann, "Medicine," June, 1903, p. 431. Hayward, "N. Y. Med. Jour.," Oct. 1, 1904. Carter, "Med. Record," May 14, 1904, p. 761. Austen, "Jour. of the Royal Army Med. Corps," June, 1904, p. 651. v. Holub, "Centralbl. f. Bakter.," Bd. xxx, p. 384. Lord, "Boston Med. and Surg. Jour.," Dec. 15, 1904. Nuttall, "Epidemiological Soc. of London," Dec. 9, 1904. Albert, "N. Y. Med Jour.," Feb. 4, 1905, p. 220. Herzog, "Amer. Jour. of the Med. Sci.," March, 1905, p. 504. Blanchard, "L'Insecte et l'Infection," Paris, 1909.

CHAPTER VII.

HYPERTROPHY, HYPERPLASIA, METAPLASIA, HETEROPLASIA, ATROPHY, HYPOPLASIA, AGENESIS OR APLASIA.

Hypertrophy may be defined as increased functional power having a tendency to persist, and that is beyond the normal for a given tissue under its existing conditions; thus, a heart weighing twelve ounces may be normal for the adult, but would be hypertrophic in a child. Hypertrophy is not simply increased size: *e. g.*, the amyloid liver may weigh six kilos and be functionally inactive. The foregoing definition also excludes tumors, which perform no useful function. Hypertrophy is usually associated with abnormal size and weight, but the reverse is not necessarily true. Many clinicians and pathologists teach that hypertrophy is essentially a structural alteration; in other words, that it is simply an increase in all the elements entering into the formation of an organ or tissue, each element retaining its normal relation to the associated structures. It is to be granted that this is true, but a definition, or even the idea of hypertrophy, based simply upon this fact alone, must of necessity be erroneous. Occasionally, one finds a tumor of the mammary gland that structurally can not be differentiated from the normal gland. The glandular elements are exactly like those normally present, but the mass is surrounded by a capsule and is sharply differentiated from the normal mamma. The normal gland being called upon for the manifestation of its associated functions, will hypertrophy, while the tumor mass may or may not show any such enlargement. It certainly produces no milk, nor are its false ducts and imitative acini connected with the normal structures. It is a new growth—something situated in the mammary gland, but having no more connection with the functions of that structure than if it were located eleswhere in the economy. The continued power to do more work than normal implies, and is nearly always associated with, an increase of the tissue performing the function; but this does not alter the fact that the essential feature of hypertrophy is power to accomplish more work than the normal organ. White[1] proposes the term **hyperergia** to be applied to those conditions in which function is increased. Hypertrophy must be differentiated from the so-called **reserve force of organs**; thus, the heart, during a period of intense excitement, may perform effectually two or three times the work that is normal for it, and still the organ may not be hypertrophied. The condition, however, does not persist; it is temporary.

Causes of Hypertrophy.—Increased work with supplied nutrition are the causes most active in extrauterine life. Examples of increased work with supplied nutrition, followed by hypertrophy, are abundant. The most familiar instance, and the one most often cited, is the hyper-

[1] "Lancet," March 9, 1901.

trophy of the heart that occurs as a result of alterations in the valves or orifices, thereby increasing the force demanded of the diseased organ. Thus, a narrowed aorta or aortic orifice may require twice the normal force to propel the blood through the abnormal obstruction. As an admirable example of increased functional power, the properly trained athlete may be cited. Evidence is not wanting to show that, under careful and continuous training, nearly all the tissues of the body may take on additional activity. These, however, fail to account for certain

FIG. 130.—HYPERTROPHY OF THE MAMMÆ.—(*Debierre, Simes' translation.*)

enormous overgrowths of organs or tissues that occasionally occur. Thus, general or partial **giant growth** may arise without any apparent extra demand for work, although, of course, the extra nutrition is supplied. This phenomenon (giant growth) has been said to arise from **congenital impulse**—an expression that only moves our ignorance of the actual cause back to a period of which we knew less concerning the functions of organs.

Still more difficult to explain are those remarkable cases of **hemi-**

hypertrophy, such as have been reported by Reismann,[1] Mackay,[2] Hutchison,[3] and many others. In these individuals but one-half of the face or one-half of the body is materially larger than the normal. In the case reported by Hutchison some of the paired viscera were affected; the left kidney weighed 56 gm., the right 28 gm.; the left suprarenal weighed 42 gm., and the right 14 gm. The case reported by Reismann is the only one of which I know in which one-half of the body was enlarged with associated enlargement of the opposite half of the cranium. Such a case strongly suggests that the central nervous system exerts some influence on the peculiar tissue overgrowth, and this view is further supported by the unilateral distribution of the lesion in many cases. Further than this we have no information upon which to base a satisfactory explanation of the condition. In some of the cases the overgrowth has been restricted to the bone, in others the panniculus adiposus alone was involved, while in still others all the tissues of the affected part appeared to participate in the change.

Since we have come to appreciate the fact that many organs perform functions of nutrition, secretion, heat production, etc., it is conceivable that some extraordinary call has been made upon them, the nature of which we can not in the present state of our knowledge estimate; this extra call may constitute the demand for additional tissue, and hence hypertrophy. There can be no apparent reason for an enormous hypertrophy of the facial and long bones, as is sometimes seen; but there must be some reason for the change, and whether this be attributed to changes in innervation or to unusual demand for some functional activity that we can not estimate (such as blood-making by the marrow) remains to be further studied. There is every reason to believe that some forms of overgrowth depend upon functional perversion on the part of one or more internal secretions. Wieting,[4] in discussing giant growth, calls attention to the well-known fact that disturbances of testicular development are often associated with perturbations of nutrition. In eunuchs the epiphyseal cartilages persist much longer than in normal males. In the giant reported by Wieting the height was 215 cm.; there was a history of hereditary syphilis and the testes were evidently immature. Exactly what internal secretion is produced by these organs and the method by which it operates, are not known. Akromegaly[5] is an affection in which it is manifest that some internal secretion, either directly or indirectly, is responsible for the condition found. The fact that the disease is frequently associated with alterations in the pituitary body or thyroid gland, and sometimes both, is suggestive.

Whatever may be the form in which hypertrophy occurs, two conditions appear to be essential: (1) The nutrition supplied must be adequate, and (2) the necessary stimulus for utilizing the supplied food is necessary. The stimulus for growth is usually brought about by a slowly advancing demand for increased work. Resting organs, no matter how well nourished, are not likely to hypertrophy; this is

[1] "Australasian Med. Gazette," June 20, 1904.
[2] "Brain," Autumn, 1904, p. 388.
[3] "Brit. Jour. of Children's Diseases," June, 1904.
[4] "Deut. med. Woch.," 1903, Bd. xxix, Nos. 21 and 22.
[5] See Part III. Chapter on Diseases of the Bones.

shown in the well-known fact that the inactive muscles in limbs treated for fracture progressively waste, and that renewed growth at once becomes evident when muscle function is resumed. When hypertrophy is to be developed by therapeutic measures, it is necessary that the work thrown upon the organ must be gradually and not suddenly increased. Overwork is invariably followed by wasting.

Hypertrophy is sometimes said to be true or false; the latter is not possible. The term false hypertrophy, or **pseudohypertrophy**, is applied to large organs in which the increase in size is not attributable to increased functional power or to increase of the elements in the normal proportions, but rather to increase in size due to the invasion of the tissues by a new element, overgrowth of some existing tissue, or some similar condition. The enlargement of the liver, associated with amyloid disease, fatty infiltration, or red atrophy, may be taken as types of so-called pseudohypertrophy. The term is a poor one, and should not be used.

Hypertrophy is said to be **simple** and **numerical**; by the former is meant an increase in the size of the cells, and by the latter, an increase in the number of cells. Kölliker has observed that the unstriped muscle-fiber of the uterus, at the end of gestation, is eleven times the length and four times the width of the normal fiber of the nonpregnant organ. Hare and Coplin, in their studies of the influence of digitalis on the cardiac muscle, note a marked increase in the transverse measurement of the fiber, an observation supported by Tangl, who found that in the ordinary form of hypertrophy of the heart there was an increase in the size of the muscle-fibers, which increase bore a definite relation to the increased weight of the organ. It is probable that in most instances of hypertrophy there is an increase in the number of cells as well as an increase in the size of the existing elements, both old and new; it is not probable, however, that both enlargement and increased number of cells are equally marked in all cases.

Physiologic hypertrophy differs from other forms of hypertrophy in that it anticipates the increased work that may be demanded of the tissue. In a certain sense all forms of hypertrophy are physiologic; hypertrophy is not a disease; but the condition referred to as physiologic hypertrophy is typified in the enlargement of the mammary glands and the increase in muscular power of the uterus in anticipation of lactation and labor. Unlike all other forms of hypertrophy, this condition apparently arises independently of existing increased work; as far as our knowledge goes, it anticipates such work.

Hypertrophy is said to be **compensatory** when one organ or tissue performs the work of another; thus, if one kidney be diseased, the opposite organ may undergo hypertrophy; if one lobe of the liver be destroyed by morbid processes, or excised, the remaining lobes may increase in size. The term compensatory hypertrophy is also used by clinicians in another sense: *e. g.*, if the orifice of the aorta has been narrowed, thereby demanding more cardiac force, and if the heart hypertrophies to meet the new condition, it compensates for the abnormal obstruction, and the hypertrophy is called compensatory. Once such hypertrophy develops, and later conditions lead to its failure, it is said that the compensation has failed; a like expression is not uncommonly used to indicate a preliminary failure. Compensatory hypertrophy de-

velops with more certainty in the young, while in extreme age the tissues commonly fail to respond to demands made for additional work.

When a tooth has been extracted, the opposing tooth becomes longer, as the result of diminished wear, and possibly of lessened resistance. This is sometimes referred to as a form of hypertrophy.

Limitations of Hypertrophy.—If the occurrence of hypertrophy depended entirely upon the demand for work, there would be no reason for its failure to progress indefinitely. Experience, however, shows that a point is always reached, sooner or later, when compensation fails, and work demanded beyond this point leads to wasting. As previously remarked, the older the individual, the earlier this occurs—a fact that suggests that the blood-vessels are responsible, to a certain extent, for the arrest of the process. It is observed in athletes that if a man has thoroughly trained early in life, he remains competent to train into "condition" throughout the major part of his days. In youth the blood-vessels are more fully capable of increasing their carrying capacity than in later years—a fact very well known of the arteries; besides, the conditions favoring hypertrophy are more marked in intrauterine life and become less effectual with advancing years. It has been shown that antenatal hypertrophy of the kidney is associated with the formation of new glomeruli and tubules, while postnatal hypertrophy evinces itself only by an increase in the size of the glomeruli and possibly in the length of the tubules.

Theoretically, once an organ begins to hypertrophy there is no reason for arrest of the process, provided the causative conditions persist or increase; but a stage is eventually reached when the blood-supply is no longer competent, the arteries being inadequate or unable to transmit the demanded additional blood. When this stage is reached, not only is hypertrophy arrested, but, if the demand for increased work be continued, wasting occurs; clinicians recognize, in the treatment of heart diseases, that, even with well-established hypertrophy and good nutrition, a stage is reached in which the best results are attained by diminishing the work to be done rather than by lashing an already overworked organ and hoping for continued hypertrophy.

Hyperplasia is an increase in the connective tissue of an organ, either associated with or independent of increase of the elements upon which the functional activity of the organ depends. If there be an increase of the functionally active cells of the organ, the increase in connective tissue must be in excess of that which is normally present, in order to be a hyperplasia. The term hyperplasia is also applied to disproportionate increase in any element of an organ. Thus, a new growth of bile-ducts is spoken of as hyperplasia; newly developed gland-cells, or an excess of one constituent of an organ without corresponding growth of the other elements, is also called hyperplasia.

Metaplasia is the direct transformation of a tissue into a dissimilar tissue. This is only possible of tissues of the same type. Different forms of epithelium may change, one into another, or one connective tissue may be converted into another, as cartilage into bone, or fibrous or loose connective tissue into fat. Transposition of type is not possible; epithelium never becomes connective tissue, nor is connective tissue ever converted into epithelium. An ulcerative process in the trachea, after cicatrization, is covered by flat epithelium from the genetic layers

of adjacent columnar epithelium, the process constituting a form of metaplasia. In order that it may be a pure metaplasia there must be no intervention of embryonic tissue. Theoretically, such a thing is possible; but whether a cylindric cell is ever actually converted into a squamous cell, without the intervention of what is essentially an embryonic cell, seems somewhat doubtful.

Heteroplasia implies the production of a tissue in some structure when such a tissue, which may be perfectly normal elsewhere, is not a normal constituent of the organ in question. The development of cartilage or bone in certain glandular structures, such as the parotid, ovary, or testicle, constitutes a heteroplasia. The best type of heteroplastic tissue is a tumor of the typic series. It will be observed that heteroplasia usually implies a change analogous to metaplasia. Thus, in the instances given the bone or cartilage found in the gland must have arisen from connective-tissue elements normally present, and, hence, probably a part of the normal gland. In such elements the proliferative change terminating in the formation of cartilage or bone implies metaplastic capacity.

Atrophy is the reverse of hypertrophy, and hence is diminished functional power, which has a tendency to persist or to increase, and which is associated with structural alterations in the tissue involved. It is not always attended by diminished size or weight, as, in the condition known as red atrophy of the liver, the organ may be considerably increased in size. Atrophy is not an arrest of development; it is an affection usually occurring in developed tissue, although an arrest in development may be followed by atrophy of the tissue that has already developed.

Causes.—Atrophy may be *physiologic: e. g.*, the atrophy of the thymus gland shortly after birth, atrophy of the uterus after labor, atrophy of the sexual organs after the menopause. The condition may be caused by *pressure*, as the pressure-atrophies of the liver. As a result of pressure from a belt or a corset, a deep fissure may be produced in the liver tissue. Again, atrophy of the hepatic structures may follow pressure brought about in other ways: for example, in red atrophy of the liver the blood-stream is retarded by obstruction to its onward flow in the heart or lungs, and gradually distends the hepatic capillaries, thereby making pressure upon the surrounding cells, which, in turn, is followed by atrophy. (See Red Atrophy of the Liver.) In the chronic indurative processes taking place in the liver the newly formed fibrous tissue, by contraction, presses upon the hepatic lobule and gives rise to atrophy. (See Atrophic Cirrhosis of the Liver.) Atrophy due to pressure is further shown in the absorption of tissues as a result of the constant pressure of an enlarging tumor or aneurysm. *Disuse* of a tissue leads to its gradual atrophy. Atrophy from disuse may be dependent upon lessened nutrition, as it is well known that the inactive tissues may be poorly nourished. This is the type of atrophy that, in generations, leads to the disappearance of tissues and organs no longer used. The wasting incident to the fixation of a limb in the treatment of fracture is in part due to its disuse, and also, in many cases, to the pressure of dressings. *Inanition*, or faulty nutrition, whether general or local, gives rise to atrophy; as examples of general atrophy due to inanition may be mentioned the progressive muscular wasting

that occurs in consumption, in the cachexia of malignant tumors, and in profound blood dyscrasias.

In the atrophies due to faulty nutrition the cellular elements having the most work to do usually suffer most. That this is not always the case, however, is shown by the extreme muscular wasting that occurs in pulmonary tuberculosis, and by the fact that the kidney and liver may not, at the same time, show any perceptible lessening in weight or in functional power. The lessened nutrition, upon which inanition atrophy depends, must not be too suddenly applied, nor must the starvation of the tissue be extreme; as a result of either of these conditions the tissue may undergo necrosis rather than atrophy. The induction of local atrophy by restricted starvation has been utilized in treatment; rapidly growing, inoperable tumors have had their growth successfully limited—for the time being, at least—by ligation of the arteries supplying them with nutrition.

Certain atrophies are spoken of as *trophic* or *neuropathic: e. g.*, atrophy associated with disease of the anterior cornu of the spinal cord; unilateral neuropathic atrophy of the face. It is presumed that certain elements in the central nervous system preside over nutrition, and that disease or injury of these elements brings about nutritive changes in the tissues over which they preside; thus, destruction of the motor cells in the cord is associated with wasting of the muscles with which the cells are connected. It is evident, of course, that here we have to deal with a complex process; in addition to the so-called trophic influence of the cells, it is necessary to consider the wasting incident to disuse of the muscles involved. The neuropathic atrophies also include muscle wasting depending upon section of the nerve supplying the affected tissues, and upon pressure, tumor infiltration, inflammation or degeneration of the motor fibers supplying the muscles that waste. Edinger[1] does not believe that the restriction of certain atrophies to definite groups of muscles depends upon any elective qualities possessed by the poison, but rather upon increased susceptibility, largely due to the fact that the particular muscles affected are those having most work to perform.

Inflammatory processes may lead to atrophy by pressure and by interference with nutrition. It is probable that the so-called inflammatory atrophies depend upon the immediate action of the irritant and properly belong with the necroses rather than the atrophies.

It is believed by some that certain substances in the general circulation may manifest a selective activity upon given tissues, thereby leading to their atrophy and absorption. Exactly how this change is brought about it is quite impossible to say, but there can be no doubt that examples apparently coming under this head occur. Atrophy of the thyroid gland during the administration of iodin and atrophy of the extensor muscles of the forearm in chronic lead-poisoning may be cited as examples of atrophic processes apparently depending upon the activity of ingested bodies or substances in other ways introduced from without.

In the cells and tissues involved in atrophy there is general shrinking of the diseased structures; the cells become granular and not uncommonly pigmented; it is reasonable to suppose that in this granular

[1] "Deut. med. Woch.," 1904, Nos. 45, 49, and 52; 1905, Nos. 1 and 4.

or fatty condition absorption of the cells is readily possible; certainly, functional activity is enormously diminished, if not, in advanced cases, suspended. In some cases the removal of wasting tissues is brought about by the intervention of cells partaking of the nature of phagocytes, It has been shown that the roots of the temporary teeth disappear under the influences of special cells applied to the exterior. Exactly how far autolysis is operative in the absorption of wasting structures is not accurately known. Langstein and Neubauer[1] have demonstrated that, at the end of gestation, the uterus contains an autolytic substance, and suggest that it is through the activity of this body that involution of the organ normally occurs.

This association of structural change with absorption and disappearance of cells has led to the name **degeneration atrophy.** It is probable that all atrophies are associated with some degenerative phenomena in the cells; by no other means can we explain the disappearance of structure. It is held, however, that atrophy is possible without appreciable cell change; such a condition has been termed **simple atrophy.** Again, the term simple atrophy is used to indicate a diminution in the size of the cells, while **numerical atrophy** implies a reduction in the number of cells. Gutch[2] finds that in brown atrophy of the heart, when advanced, the muscle-fibers are conspicuously reduced in size, and it is a common observation that in wasted organs, in which the atrophy is uncomplicated, the affected cells are smaller than normal. It is probable that in nearly all atrophic processes reduction both in size and number occurs.

When the atrophic phenomena are due to the inability of the cell to assimilate supplied nutrition, the lesion is said to be an **active atrophy;** when the fault lies in deficient nutrition, the condition is called **passive atrophy.** The same cause acting upon different tissues may give rise to atrophy in some and not in others. Again, two tissues, apparently similarly placed with regard to nutrition, may show different degrees of atrophy, although the indications are that the cause acts equally upon the two elements; thus, the connective tissue of glands wastes slowly, while, in the presence of the same causal factors, the parenchymatous structure may show a far more marked atrophic change.

Hypoplasia differs from atrophy in that development has been arrested either before or after birth; it is not wasting of tissue, but failure to reach the normal development. The process may involve the whole body, or it may be restricted to one or more organs or parts of organs, or to the organs belonging to a single system; as, for example, hypoplasia of the genital apparatus. Dwarfs are examples of hypoplasia. **Symptomatic infantilism** is applied to individuals whose growth has been stunted by malnutrition or disease. **Ateleiosis** is a form of developmental disorder characterized by the persistence of child-like peculiarities in adult life. Gilford[3] recognizes two forms of the affection; in the **asexual ateleiosis** the developmental arrest, in addition to other structures, also involves the sexual organs, which undergo no further evolution after the abnormality is inaugurated. The degree of the arrest is determined by the age at which it begins. It may originate before

[1] "Münch. med. Woch.," July 29, 1902.
[2] "Jour. of Path. and Bact.," June, 1901.
[3] "Brit. Med. Jour.," Oct. 8, 1904, p. 914.

birth, in infancy or early childhood, or even late in adolescence. The sexual organs retain the characteristics present at the time the affection began; in one of Gilford's cases a boy aged twelve years possessed generative organs no further developed than those of an infant at birth. In this condition the resemblance to true infantilism is strong. In **sexual ateleiosis** the dwarfing is general except that the generative organs, at maturity, are developed as usual. With this group belong some of the celebrated dwarfs, such as Tom Thumb and his wife, Commodore Nutt, Minnie Warren, and others. The head, limbs, figures, and facial characters are those of childhood. **Nanism** and **nanosoma** are terms applied to dwarfs without any special consideration as to the character of the dwarfing. Of the causes of these and allied conditions little is known. In cretinism[1] there is absence, or hypoplasia, of the thyroid gland associated with arrest of growth and other important nutritional disturbances; the affection is amenable to treatment by thyroid substance or extract. Cretins, although small of stature, are not dwarfs in the scientific comprehension of the term, nor is dwarfism to be regarded as a manifestation of the cretinoid state.

When hypoplasia is not universal but is restricted to one side of the body or one-half of an organ, as the brain (some types of microcephalus), it is known as **asymmetric hypoplasia.** The cause may lie in incomplete development, or partial occlusion of the blood-supply to the tissues involved. This not rarely proves to be the case where syphilitic endarteritis has lessened the blood-supply to an organ or a part of an organ; an example of the first is sometimes seen in the kidney, and of the latter in the liver. The environment of organs may lead to hypoplasia, as when bands of inflammatory tissue restrict their growth, or failure in the development of the skull limits the increase in the size of the brain. The growth of an organ may be arrested by destruction of the nervous mechanism presiding over its functions. Thus, if the ganglion cells in the anterior cornu of the spinal cord, in the area supplying a member or parts of a member, be destroyed (anterior poliomyelitis) early in life, subsequent development of the affected structure is interfered with or absolutely arrested. Still other types of hypoplasia must be traced to fetal anomalies.[2]

Agenesia, agenesis, or **aplasia** should be restricted to mean entire failure of development: that there has been no effort at the production of an organ or tissue. This is seen in the kidney at times, and is usually due to obliterative disease of the renal artery. The term is also applied to the disappearance of partly developed organs. It may be used to indicate the failure of a given structure of an organ to develop. As an example of the latter, occasionally the fibrous skeleton of an organ is fully mature without any corresponding development of the parenchyma, in which case there is said to be agenesis of the parenchyma.

[1] See Part III, Diseases of the Thyroid Gland.
[2] See Achondroplasia, Part II, Diseases of the Osseous System. Also Poncet and Lereische ("Revue de Chir.," Dec. 10, 1903, p. 657) and Peloquin (Thesè de Lyon, 1902–1903, No. 22).

CHAPTER VIII.

INFILTRATION AND DEGENERATION.

(A) INFILTRATION.

Infiltration is the "filtering in," or deposit in organs, of some substance not normally present, or an excess in quantity of a material that normally constitutes a part of the affected tissue. It will be observed that the term "infiltration" is here applied to a material and not to a tissue, although one must confess that the difference is not striking. If tissues are included as infiltrating bodies, then a tumor invading an organ would be an infiltration; such is not the meaning of the term in the sense here used. The materials studied in the infiltrations are chemic substances, rather than tissues possessing definite histologic structures. Thus, fat, lime salts, the various pigments, glycogen, and even amyloid material, are bodies with definite chemic composition, and not composite mixtures of many agents, as are the tissues. It is true that amyloid material has a rather characteristic histologic structure and stain reaction; so have many crystals, but this does not make them tissues, in the common acceptation of the term. Infiltrations are (1) fatty; (2) amyloid or albuminoid or, possibly more correctly, lardaceous; (3) pigmentary; (4) calcareous; (5) glycogenic.

1. **Fatty infiltration** consists in the addition of fat to an organ in which fat is not normally present, or a notable increase in the amount of fat in an organ that normally contains less. The recent studies of Taylor,[1] Shattock,[2] Ribbert,[3] and Arnold[4] review in detail the arguments for and against recognizing fatty infiltration and fatty degeneration as distinct processes. The tendency to speak of fatty infiltration as normal fatty degeneration, and to regard the change usually designated fatty degeneration as an exaggerated manifestation of the first-named condition, seems confusing and offers no advantages over previous custom.

Under certain conditions the deposit of fat may properly be considered as physiologic. This same deposit, however, carried to excess may interfere with the nutrition and function of the involved or adjacent tissues, and when this stage is reached, the process becomes essentially pathologic. As evidence of the physiologic deposit of fat one need but cite the fat normally present in the hepatic cell, which is apparently necessary for the proper functions of that structure. A certain amount of fat is normally contained in the subcutaneous tissue, in the orbit, in the perirenal tissues, and elsewhere. Physio-

[1] "Amer. Jour. of Med. Sci.," 1899, vol. cxvii, p. 569.
[2] "Jour. of Path. and Bact.," Dec., 1903, p. 234.
[3] "Deut. med. Woch.," vol. xxix, p. 44.
[4] "Virchow's Arch.," Bd. 171, also "Münch. med. Woch.," Oct. 27, 1903, p 1857.

logically, the fat deposited in the areas named may perform a number of functions: the first, and probably the most important, function is the storage of reserve food that may be called upon when the usual source of nutrition for any reason becomes inadequate. The fat in the orbit as well as that around the kidney acts as a cushion, offering to the adjacent organ a certain amount of protection from injury.

Causes.—Increased nutrition: decreased work; slowed circulation; reduced or faulty oxidation. In increased nutrition fat is stored in the tissues being in excess of the quantity that the cells can utilize for existing demands. If the functional activity of the cell be reduced by lessened demand, and the normal amount of blood is sent to the cell, the nutrition is in excess, and fatty infiltration may result. Moderate

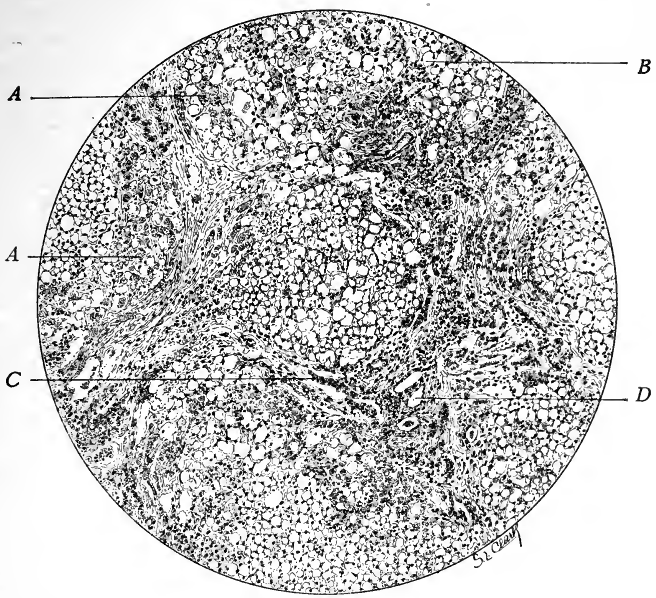


FIG. 131.—LIVER SHOWING CIRRHOSIS WITH ADVANCED FATTY INFILTRATION.
Death was the result of croupous pneumonia and, therefore, an added granular degeneration (cloudy swelling) of the few previously unaltered liver cells is present. *A*, *A*. Groups of granular liver cells. *B*. Liver cell, the protoplasm of which is almost completely replaced by fat. *C*. Imperfectly outlined bile-duct. *D*. Portal branch surrounded by the newly formed fibrous tissue.

retardation of the circulation gives rise to fatty infiltration; thus, slowing of the circulation partly accounts for the fat infiltrated into the connective tissue of the omentum and mesentery in cirrhosis of the liver, and also for the fatty infiltration that occurs in the liver lobules in cirrhosis.

The infiltration of fat occasionally observed in the liver in tuberculosis, and associated with marked emaciation, and the infiltration seen in the subcutaneous tissues in chlorosis, where the blood findings would certainly indicate that nutrition is not in an ideal condition, are taken to be examples of fatty infiltration depending upon faulty oxidation.

The origin of the stored fat has been a matter of much discussion. It is now generally conceded that it may arise from a number of sources. In the fatty deposits of hypernutrition it is usually held that it represents the fats and sugars in the food, and, to a limited extent, the albuminoids. In deposits from other sources it is not improbable that the albuminoids are more important as sources of the fat than the usual food-products to which it is attributed.

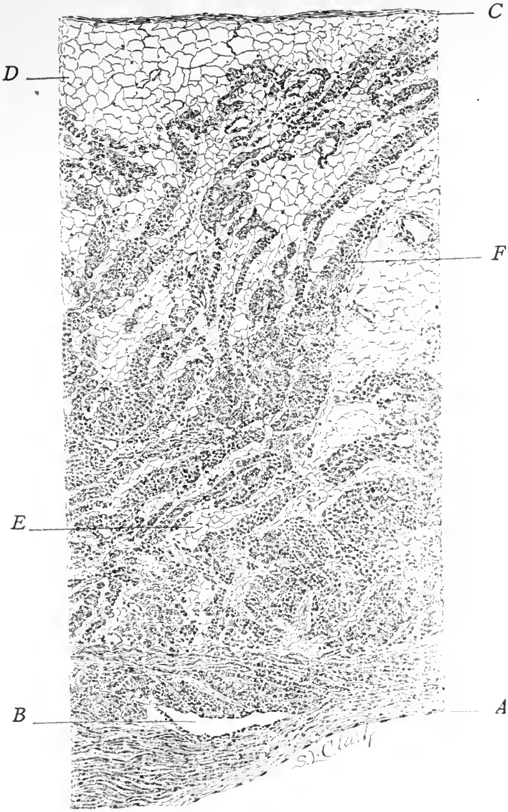


FIG. 132.—HEART EXTREME FATTY INFILTRATION.
A. Endocardium. *B.* Vein in myocardium. *C.* Epicardium. *D.* Subepicardial fat. *E.* Irregularly distributed through the myocardium from just above the leader from *B* nearly to *C* are columns of fat as shown at *E.* *F.* The infiltrating fat separates the muscle into irregular bands such as may be seen at *F*, but becoming thinner above and thicker below this point.

Sites.—The cells normally containing fat as one of their essential constituents are first to show excessive deposit of the material when changed conditions lead to infiltration. This is observed in the liver, particularly in the peripheral zone of the liver lobule; in the general subcutaneous tissues, with the exception of the lax areolar structures of the scrotum and eyelids, and of the lips, alæ of the nose and ears; in the connective tissue between the muscle-fibers (pseudohypertrophic muscular paralysis, Fig. 133); in the subserous structures; and in other connective tissues. A more or less circumscribed collection of fat constitutes a neoplasm known as a lipoma (see Tumors). The general infiltration of fat into an organ—such, for example, as the heart—is referred to as **lipomatosis,** or **adiposis,** of the tissue involved. When the infiltration of fat is extensive, constituting what might be termed a universal lipomatosis, the condition is commonly spoken of as **obesity** or **adiposity.** Dercum first described a peculiar form of general lipomatosis associated with pain and other nervous phenomena, and the condition is now generally known as Dercum's disease. At first the fat deposits appear to be limited, but later may become extensive. The affected areas are tender and there is tenderness over the nerve-trunks. Some of the muscles may give the reac-

tions of degeneration. In consideration of the tenderness and pain Dercum proposed the name **adiposis dolorosa.**

Microscopically, in the subcutaneous and areolar structures, the fat is taken up by the connective-tissue cell; the nucleus is crowded to one side, the fat existing in the cell as a single large oil-globule; in the liver the fat is stored in the hepatic cell. The nuclei of the infiltrated cells are not diseased, but displaced to one side, the "signet-ring" appearance. In the muscles the fat is infiltrated between, and not into, the muscle-fibers, a condition easily differentiating fatty infiltration from fatty degeneration. It is not intended to imply that fatty infiltration is always essentially a simple process; not uncommonly it is combined with an associated fatty degeneration, the two conditions being so intermingled as to lead many observers to hold that they are essentially similar. There can be no doubt that fatty infiltration may exist independent of fatty degeneration, and that the reverse is equally possible. As the degenerative process is the graver, the infiltration is less important in the mixed lesion.

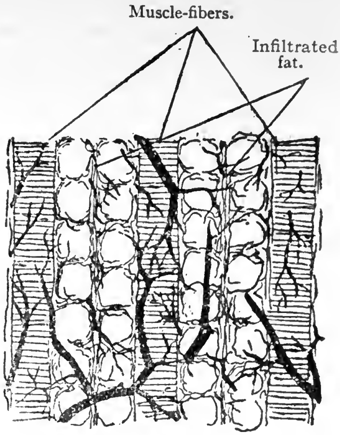


Fig. 133.—Pseudohypertrophic Muscular Paralysis; Fatty Infiltration of Muscle.—(*Flütterer.*)

2. Amyloidosis, amyloid or **albuminoid infiltration,** also known as albuminoid disease, lardaceous infiltration, waxy or bacony infiltration. Of the many names applied to this condition, the term lardaceous offers

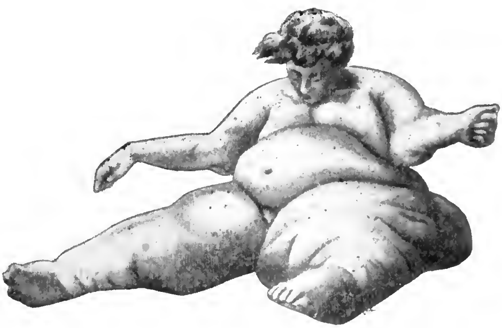


Fig. 134.—Universal Lipomatosis
From photograph taken at autopsy. The cadaver weighed 540 pounds.

certain advantages and has the official sanction of the Royal College of Physicians; to avoid the confusion incident to our ignorance in regard to the ultimate character of the processes it is deemed most wise to avoid calling it either an infiltration or a degeneration, and for the present to refer to it as lardaceous change or

lardaceous disease.[1] Amyloid material, or, more properly, lardacein, is found during health in the prostate gland, and has been observed in the pia mater.

Causes.—Amyloid material probably represents an altered proteid normally present in the blood—possibly fibrin, or, more correctly, the proteid body or bodies whose end is in fibrin. It can be produced artificially by suspending the spinal cord in alcohol for a few months. The artificial product so made responds to the chemic tests for lardacein, and can not be differentiated from the natural material. If fresh blood be whipped, and the fibrin so obtained washed and treated with a 1:2000 solution of hydrochloric acid, the mass becomes gelatinous, clear, and pultaceous, and responds to all the stains for amyloid material. As

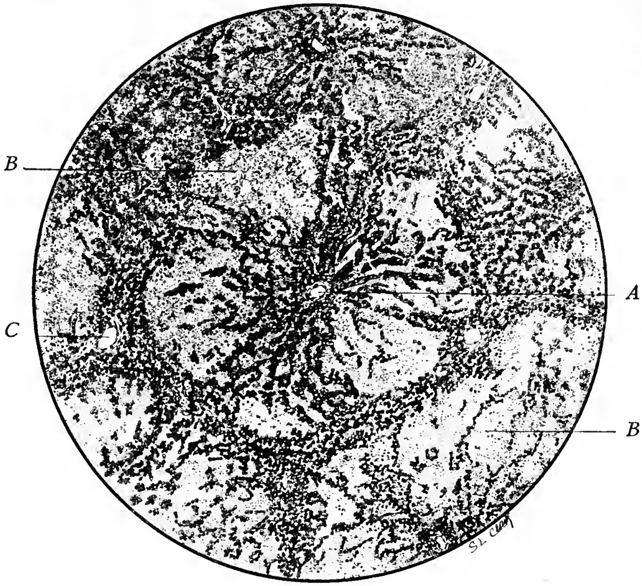


FIG. 135.—LIVER SHOWING FAIRLY ADVANCED LARDACEOUS DISEASE; THE ORGAN WEIGHED 17 POUNDS. *A*. Central vessel of lobule surrounded by considerable residual liver tissue; the periphery of the lobule with corresponding parts of adjacent lobules also persists. *B*, *B*. Lardacein. *C*. Interlobular vessel.

amyloid infiltration commonly occurs in connection with long-standing suppuration in which the alkaline salts are drained in excess, and as the product resembles a dealkalinized fibrin, it was supposed that the morbid process naturally arose as a result of the removal of alkaline

[1] The important recent literature concerning lardaceous disease will be found in, or may be traced from the following articles: Schmidt, "Centralbl. f. allg. Path. u. path. Anat.," Jan. 31, 1905, p. 49. Monery, "Jour. Phys. et path. Gen.," Sept. 15, 1902. Minkowski, "Zeit. f. klin. Med.," 1901, Bd. 45, Heft 5 and 6. Browicz, "Przeglad lekarski," Nos. 43–44, 1901. Litten, "Berlin klin. Woch.," Dec. 17, 1900. Green, "Jour. Path. and Bact.," Feb., 1901. Blum, "Wien. klin. Woch.," March 19, 1903, p. 349. Godlee, "Lancet," Dec. 5, 1903, p. 1551. Edens, "Zeig. Beitr.," xxx, H. 2, 1904. Neuberg, Ueber Amyloid., "Verhandl. d. Deutschen. pathol. Gesellsch.," Jahrg. 1904, No. 1, pp. 19–32.

salts from the blood; this view is not borne out, however, by the fact that lardaceous disease occurs in malaria and syphilis, sometimes unassociated with suppuration. Tuberculosis is often a cause (50 per cent. of the cases), especially bone and lung tuberculosis. Anything that greatly reduces the general nutrition favors its development. Among the many careful studies bearing on the relation of other diseases to the occurrence of amyloid, those of Wicht (1887) and Blum (1903) merit special mention. Blum's observations are based on 18,153 autopsies, in 279 of which he found lardaceous disease. Only 5 of the patients were under ten years, and over 200 were between twenty and fifty years of age; 141 were males. Blum found that tuberculosis was the cause in 79.2 per cent.; in Wicht's series 59 per cent. were tuberculous. Wicht traced 10 per cent. to syphilis; Blum only 2.9 per cent. Blum made the interesting observation that 25 per cent. of the patients having actinomycosis also had amyloid disease. Practically all patients with amyloid disease show more or less anemia.

By some, lardaceous disease is regarded as a degeneration. In a sense this is true; in the blood the alteration is of the nature of a degeneration; the material itself is a degeneration product, as, probably, is melanin. As deposited in organs, it represents an additional element —an infiltration; and as the degenerative process is restricted to the origin of amyloid material, the term infiltration is applied to the deposit in organs and tissues. There is not adequate proof that, where found, it results from a degenerative change in the tissues at hand: *e. g.*, it is not probable that the amyloid liver weighing 7 kilos is the result of a degenerative change in an organ normally weighing less than 2 kilos. Wherever found, lardacein presents evidence of being an added product; but as to the method by which the addition is accomplished, we know but little. It may be that primarily there is a deposit of some body that later is converted into lardacein.

Attempts at the artificial production of amyloid infiltration by the injection of bacteria or of bacterial products into animals have not yielded uniformly successful or satisfactory results. Krawkow's experiments were unsatisfactory, in that the artificial lesions did not resemble, with any detail, the disease as seen in man. Later experiments by Davidsohn seem to have been more successful. Green[1] has produced an amyloid substance by infection with pure cultures of staphylococci, but the results are not convincing. The artificial production of amyloid disease must be considered, for the present at least, as being in the experimental stage.

Sites.—The process usually begins in the blood-vessels, deposition taking place in the intima and between the intima and adventitia, displacing, or, to a certain extent, replacing, the muscular coat. The deposit occurs almost exclusively in the arteriole, but may be seen around the capillaries, and occasionally in the larger blood-vessels. The organs most commonly involved are the liver, the spleen, the kidneys, the blood-vessels of the mucous membranes,—more particularly those of the intestines,—and the lymph-nodes. Of 118 cases of lardaceous disease observed by Dickinson, the reaction was present in the kidney in 95; in the spleen in 76; in the liver in 65; in the intestines in 35; in the stomach and suprarenals, each 9; in the lymph-nodes

[1] "Jour. of Path. and Bact.," Feb., 1901.

in 5; in the pancreas, thyroid, esophagus, testis, and endocardium, each 1. In 279 cases studied by Blum the spleen was involved in 92.5 per cent., the kidney in 81 per cent., the liver in 62.7 per cent., the intestine in 21 per cent. Godlee is of the opinion that when the cause of the disease (for example, persisting empyema) is removed, complete recovery may occur.

An interesting form of lardacein deposit is represented by the so-called **amyloid tumors** which often arise independently of wide-spread inflammatory or suppurative processes. These masses are found in the conjunctiva, eyelids, lymph-nodes, upper air-passages,[1] and occasionally in tumors. Localized lardacein collections may be found in and around gummas. Steinhaus[2] records a case in which amyloid and hyaline infiltrations involved the myocardium in the form of nodular accumulations. Similar nodules occurred in the submucosa of the stomach and intestines.

Morbid Anatomy.—The amyloid organ is large, heavy, and pale, the paleness being due to the infiltrated material and to the anemia; the borders, if previously sharp, are rounded; it is tough in texture; decomposition takes place very slowly; and the organ possesses a specific gravity very much higher than the normal. In the spleen the Malpighian bodies are largely involved, and usually show as small translucent grains, resembling boiled sago, and hence the name "sago-spleen." (For description of morbid anatomy of lardaceous disease of the liver, spleen, kidney, etc., see chapters on those organs in Part III.)

Chemic Tests and Reactions of Amyloid Material.—Amyloid material is but slightly digested by pepsin, and only when presented in a finely divided state. It is soluble in ammonia and in strong hydrochloric acid, but is not dissolved by dilute mineral acids or by acetic acid, or in saline solutions, or in water. The iodin reaction, which is usually applied for the detection of amyloid material, is obtained as follows: A watery solution of iodin, such as Gram's solution (iodin 1 part, potassium iodid 2 parts, water 300 parts), is applied to the cut surface of the suspected organ, first carefully washing away any blood that may be present. The amyloid material is stained a mahogany-brown (see Plate V), while the normal tissue takes on a canary-yellow color. If a small piece of tissue be stained with iodin, as previously directed, and afterward treated with a five to ten per cent. aqueous solution of sulphuric acid, the lardaceous material reddens and eventually turns blue. Occasionally, this reaction can not be obtained, the sulphuric acid deepening the brownish hue already given by the iodin. The fact that amyloid material does not always respond in exactly the same manner has led to the belief that we are dealing with a number of bodies so closely allied that, with the means at present at our command, differentiation is impossible.

For the histologic demonstration of lardacein the material should be fixed in absolute alcohol, the sections stained in Gram's solution, washed in water, and mounted in glycerin or glycerin jelly. Unfortunately, permanent mounts quickly lose the characteristic color. Sections may be, without previous staining, dehydrated in a mixture com-

[1] See Manasse, "Virch. Arch.," 1900, vol. clix, p. 117.
[2] "Zeitschr. f. klin. Med.," vol. 45, Nos. 5 and 6.

Cut surface of spleen, showing lardaceous change. The wedge-shaped area shows the iodine reaction. (*Atlas of Pathology*, Sydenham Society.)

posed of one part of tincture of iodin and three parts of absolute alcohol, cleared, and mounted in oleum origani cretici. A number of anilin dyes afford reasonably characteristic stains for amyloid material. Sections are stained in a one per cent. solution of methyl-violet for five minutes, washed lightly in one per cent. aqueous solution of acetic acid, followed by water to remove the excess of the acid, and mounted in glycerin or glycerin jelly. The tissues by this method are stained blue and the amyloid material a reddish-violet. Iodin-green may be applied in the same manner, although a longer time in the stain is usually demanded; with this reagent the tissue stains green, the lardacein, reddish-violet. Birch-Hirschfeld recommends a combination of gentian-violet and Bismarck brown. Sections are first stained five minutes in a two per cent. alcoholic solution of Bismarck brown, washed in alcohol followed by water, and this in turn by a two per cent. aqueous solution of gentian violet for ten minutes; they are differentiated in one per cent. aqueous solution of acetic acid, washed in water, and mounted in glycerin or glycerin jelly, or, best, in levulose. The tissue is stained brown by this method and the amyloid material red. Harris recommends the following method: Fix material in alcohol, stain sections three to twenty-four hours in carbol-toluidin-blue, rinse with water, and mordant for one or two seconds with a two per cent. solution of ferrocyanid of potassium, wash in water, and differentiate in acid alcohol. Dehydrate, clear in cedar oil, mount in balsam. Lardacein is stained red; other elements, varying shades of blue; the slightly reddened fibrous tissue is easily identified. In addition to the specific stains previously indicated, satisfactory exhibition of the amyloid areas is afforded by any good hematoxylin stain, followed by eosin and mounted in the usual manner. Sections so prepared keep well and exhibit both the normal and abnormal structures to advantage.[1]

3. **Pigmentary infiltration,**[2] also known as **pigmentation,** consists in the introduction into, or production by, the tissues or cells of pigment granules. These pigment granules may arise from two sources: (*a*) They may be imported into the body, and are therefore **extraneous pigments,** or (*b*) they may arise as the result of changes in elements normally present in the body—**autochthonous pigments.** Another form of pigmentation, known as **pseudomelanosis,** has been described; it is due to hydrogen sulphid coming in contact with the iron present in the tissues postmortem. It is usually seen on the under surface of the liver, and occasionally on the intestines; sometimes the spleen is intensely colored. One aware of its possible occurrence postmortem is not likely to be mistaken, or fail to recognize the condition when it is present.

[1] A very full bibliography of amyloid disease is given by Chantemesse and Podwyssotsky, "Les Processus Généraux," 1901, p. 208.

[2] Exhaustive bibliography on Pigmentations, see Chantemesse and Podwyssotsky, "Les Processus Generaux," 1901, p. 313. Also Oliver, "Lancet," Nov. 14, 1903, p. 1245. Tendeloo, "Münch. med. Woch.," Aug. 30, 1904, p. 1537. Hessler, "Amer. Med.," Oct 1, 1904, p. 590. Sehrt, "Virch. Arch.," 1904, Bd. 177, p. 248. von Furth, "Centralbl. f. allg. Path. u. path. Anat.," Aug. 15, 1904, p. 617. Falckenberg, "Centralbl. f. allg. Path. u. path. Anat.," Sept., 1904, p. 662. Parker, "Brit. Med. Jour.," Oct. 24, 1903, p. 1052. Osler, "Lancet," Jan. 2, 1904, p. 10. Solman, "Jour. Path. and Bact.," Feb., 1901. Beattie, "Jour. of Path. and Bact.," Aug., 1903, p. 117.

(*a*) *External or Introduced Pigments.*—These are well illustrated in pneumoconiosis. (See Diseases of the Mucous Membranes in Part III.) In this type are included solid pigments arising from external sources, such as hard coal in miners, iron in laborers in iron manufactories, and, in stone cutters, particles of sand. Any of these insoluble pigments can secure access to the tissue through a wound, in which they are probably retained by the action of phagocytes. A form of this pigmentation, as it occurs in wounds, is seen in tattooing, also in the small grains of powder that may be forced into the skin in powder explosions.

In **pneumoconiosis** the foreign material enters by way of the air-passages, and may consist of any solid body that is capable of dissemination in a sufficiently finely divided state to permit its inhalation. When the solid material is hard coal, the condition is spoken of as **anthracosis**; when the material contains iron, the affection is known as **siderosis**; when composed of sand or of fragments of stone, as in stone-cutters, it is called **lithosis** or **chalicosis.** Potter's pneumoconiosis—

Fig. 136.—Section of Lung Showing Infiltration of the Connective Tissue of the Alevolar Wall by Coal-dust (Anthracosis).—(*Rindfleisch.*)

kaolinosis—results from the inhalation of kaolin, a clay used in the manufacture of pottery. Dust pigmentation of the lung also occurs in street sweepers and in the workers in shoddy mills, granaries, and other dust occupations. The inhaled foreign body is less likely to give rise to important tissue changes than the associated bacteria which accompany it or later enter the affected tissues. Of the inorganic substances, Reckzeh holds that lime is the least injurious. Dusts of organic origin, such as wool and hair, are the most dangerous. Once the pigment passes through the protecting membrane,—either skin or mucosa,—it reaches the lymphatic spaces, and may pass on to the lymph-nodes, or even further, eventually reaching the circulation. A lymph-node may break into a blood-vessel, and the solid pigment may be carried everywhere by the circulation. Weigert asserts that this is a method by which any extraneous pigment reaches other viscera than the lung; *e. g.*, the liver and spleen. Betz reports the case of a stone-cleaner whose urine suddenly contained an easily

sedimented black pigment which was present in demonstrable quantities for four days. The carbonaceous character of the substance was demonstrated by chemic examination.

Other extraneous pigments do not enter the body as pigments, but are converted into pigments by the action of the body-juices. Silver may be taken as a type of these pigments entering the circulation and coming to the surface of the body as an albuminate. It is deposited in the skin by the action of light as metallic silver, the resulting condition being known as **argyria.**

(*b*) *Pigments Derived from Elements Normally Present in the Body.*—Pigmentation is a normal process in the skin of the negro, and in the iris, etc. Pigments derived from the blood—so-called *hematogenous pigments*

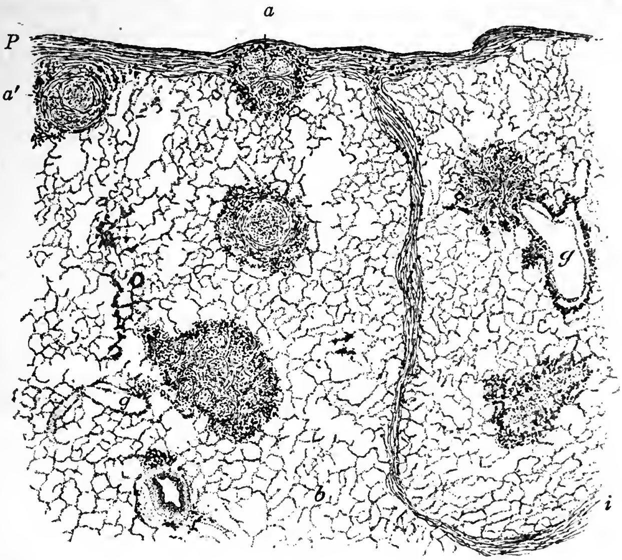


FIG. 137.—SECTION OF A LUNG SHOWING CHALICOSIS.

P. Pleura. *b*. Nearly normal air vesicles; some are slightly emphysematous. *a*. Mass of infiltrated material with dense fibrous capsule and situated in the pleura. *a'*. Similar mass in the lung tissue; other masses are shown. *g*. Blood-vessel around a branch of which is forming an area of infiltration. *i*. Thickened fibroid, interlobular septum.—(*Schmaus*.) × 30 diameters.

—are the results of changes in the normal hemoglobin during life. In health the hemoglobin is not yielded to any of the tissues with which it comes in contact; in certain conditions, however, the stroma of the erythrocyte containing the normal pigment may be altered or destroyed (hemolysis), giving rise to **hemoglobinemia,** or the hemoglobin may pass off with some of the excretions, as in **hemoglobinuria.** During life the two blood pigments resulting from changes in the hemoglobin are *hematoidin* and *hemosiderin;* the latter differs in many respects from the former: the principal difference is that hemosiderin contains iron. A pigment very closely allied to those just mentioned is *melanin;* with hemosiderin, melanin forms the chief pigment of malaria. Melanin is a normal pigment in the skin of the negro and around the nipple in the white; it is

also seen in tumors, where the condition is known as *melanosis*, or the tumor is said to be *melanotic;* it may be produced by the cellular activity of the part, and it may follow hemorrhage. In malaria melanin may be found in the large glandular viscera, such as the liver, spleen, and kidney, and also in the brain. Rogers has recently called attention to a peculiar pigmented atrophy of the mucous membrane of the small intestine in cases of malaria. In some instances the pigment deposit is sufficient to render the mucosa gray or of a dark, slaty color.

In 1889, von Recklinghausen described a form of pigmentation affecting a number of organs which he called **hemochromatosis.** Opie[1] has very fully studied the condition and collated the literature. Many glands in the body are impregnated with a reddish-yellow or ochre-colored, granular pigment, containing iron. The muscularis of the stomach and intestines contains a fine, pure yellow, granular, iron-free pigment. The granules containing iron are called *hemosiderin*, the others *hemofuscin.* The condition is associated with cirrhosis of the liver and chronic interstitial pancreatitis. The bronze diabetes of the French appears to be a terminal stage in the affection.

Ochronosis[2] is characterized by the deposit of black, or brownish-black, iron-free pigment in the cartilages. It is usually associated with melanuria. The source of the pigment and the cause of its presence in the urine remain undetermined.

In Addison's disease[3] there is an excess of pigment in the rete and deposits may also occur in the mucosa, particularly of the mouth. The source and character of the pigment are not definitely known, although it is reasonable to suppose that it is a hemoglobin derivative.

Jaundice.[4]—A form of pigmentation in which the pigment is derived from blood coloring-matter, but which, at the same time, would not occur without the intervention of another process in metabolism, is jaundice. Jaundice is not properly considered with the infiltrations of pigment; it is more truly the diffusion of a soluble pigment. Its action however, on many cells closely resembles that of insoluble pigments While it is true that certain blood pigments, including hematoidin, are chemically identical with bilirubin, and that the latter is abundantly formed when there is rapid hemolysis, still there is not sufficient reason for believing that this production is ever sufficient to give rise to jaundice. Bile pigment is produced in the liver, and by reabsorption enters the circulating blood, and is the agent that gives rise to the discoloration of the various tissues so markedly influenced in jaundice. The pearly white of the conjunctiva is usually first to manifest the discoloration; afterward all of the tissues become more or less discolored.

[1] "Jour. of Exper. Med.," vol. iv, 1899, p. 279.

[2] Heile, "Virch. Arch.," 1900, Bd. clx. Albrecht, "Zeit. f. Heilkunde," 1903, vol. xxiii, Nos. 10 and 12.

[3] See Diseases of the Adrenals.

[4] Sandwith, Cantlie, Anderson, and also Mathias, "Brit. Med. Jour.," Sept. 17, 1904, pp. 672 to 678. Anders, "Amer. Jour. of Med. Sci.," April, 1903, p. 596. Sacquepee, "Arch. de med. Exper. et d'Anat. path.," July, 1902. Jagic, "Ziegler's Beiträge," 1903, vol. xxxiii, p. 302. Joannovics, "Zeit. f. Heilk.," 1904, vol. xxv, p. 25. Pick, "Wiener klin. Woch.," vol. xvi, No. 17. Ravenna and Gentili, "Lo Speriment.," Feb., 1904. Cocking, "Quarterly Med. Jour.," Yorkshire, Feb., 1903, Eppinger, "Beitr. zur path. Anat. u. zur all. Path.," 1903, vol. xxxiii, p. 123. Phillips ,"Lancet," June 27, 1903, p. 1796. Hutchinson, "Practitioner," Feb., 1902.

Commonly, the brain and spinal cord escape pigmentation. It is said that the gastric and pancreatic secretions do not show the yellowish tinge. With regard to the sources of the pigment circulating in the blood two views have long been in force, these leading to the recognition of two forms of jaundice, one hepatogenous and the other hematogenous.

Hepatogenous jaundice depends upon the production of bile pigment in the usual way, and its absorption by the blood as a result of retention within the biliary channels. This retention may depend upon swelling of the mucous membrane of the duct, biliary calculi, tumors within or without the duct and pressing upon it, inflammatory adhesions, kinks, pressure by a misplaced viscus, such as the right kidney, parasites in the bile-duct, etc. The resorption of bile as a result of such obvious obstructions as those just considered deserves no special comment. There are forms of jaundice, however, that are not obstructive in the sense previously indicated. It is alleged that jaundice may depend upon the overproduction of bile (polycholia); the abnormal bile may be viscid, slow-flowing, and hence offer opportunities for resorption, or, entering the intestine in large quantities, it may be taken up by the portal circulation and returned to the liver, which may not be equal to the continued removal of the pigment from the blood, which, escaping the hepatic cells, passes onward into the general circulation. Although the obstructive origin of all forms of jaundice has been generally accepted, there has not been uniform agreement as to the route by which the bile elaborated by the liver cells enters the circulation. The recent studies of Eppinger, Winckelmann, Abramow, and Samoilowicz indicate that absorption takes place through the lymphatics of the liver.

Hematogenous jaundice is seen in connection with various morbid processes in which blood destruction constitutes an important element. It is the erythrocytolysis (hemolysis) of yellow fever, pyemia, pernicious malarial fever, and allied diseases that causes the form of jaundice in question. The jaundice associated with venom-poisoning, phosphorus-poisoning, etc., belongs with this group. The fortunate possession of an agent (toluylenediamin) destroying the blood and bringing about this form of jaundice has enabled investigators to study the changes that accompany the condition. It has been shown that destruction of the blood-cells leads to the production of a bile the viscosity of which prevents rapid flow through the biliary capillaries, and hence permits regurgitation, or at least increases biliary pressure to an extent compatible with resorption. At the same time there is more or less catarrhal swelling of the mucosa of the biliary passages, which further impedes the flow. The jaundice is then truly obstructive, and not actually of hematogenous origin, although the initial step in the process was probably the erythrocytolysis. Experimental studies of the jaundice produced by phosphorus and arseniureted hydrogen offer conclusive evidence that the production is due to the same conditions as toluylenediamin jaundice. Further, it has been shown that if the liver is removed and poisoning by some of the before-mentioned agents brought about, blood pigments appear in the urine, though bile pigments are not found.

A number of writers have described a form of jaundice, sometimes epidemic, suggesting communicability. Such systematic writers as

Strumpell, Loomis, and Thompson refer to it. Pomeroy reported an epidemic in Calumet, Michigan. Costa describes 70 cases occurring among soldiers where the evidence of contagion appeared to be clear. Nicolaysen[1] reports an epidemic of 123 cases and believes that the condition depends upon a specific gastro-intestinal catarrh transmissible from person to person and often occurring without its associated jaundice. The infectious jaundice described by Sandwith, the epidemic catarrhal jaundice reported by Anderson, and the jaundice of the tropics, are evidently closely allied affections. The relation of these to one another and to Weil's disease is not known; all are attended by more or less marked jaundice, and hepatic and, usually, splenic enlargement. A number of bacteria have been described as occurring in the condition, but no specific organism has been isolated.

A pigment closely allied to hematoidin is *lutein*, which is the coloring-matter of the yolk of the egg, and is found in the corpus luteum. Lutein and a number of pigments appear to be rich in fat and have been designated *lipochromes*, placing them with the coloring-matter of normal adipose tissue.

There are a few pigments that do not enter the body as such, but are developed in the body from elements not normally present; as an example of these may be mentioned the pigmentation following the administration of silver, *argyria*, to which reference has already been made.

Bacterial Pigmentation.—Certain pigments produced by bacterial growth occur in suppuration. The bacillus pyocyaneus is the organism most commonly producing pigment in pus, or even catarrhal discharges from such mucous surfaces as the nose, uterus, and, rarely, the bowels.

Occasionally, the cells whose particular function it may be to elaborate given pigment fail to do so. Such failures often become as conspicuous and as easily recognizable as the overproduction of pigment under other circumstances. The **albino** is an example of congenital absence of pigment production, particularly in the skin, the hair, the irides, and the choroid coats of the eyes. A minor degree of failure in pigment formation is seen in the condition spoken of as **leukoderma,** in which whitish areas appear upon a skin otherwise normal. Occasional instances of this peculiar disorder have been observed in the colored race, the skin at times showing areas of snowy whiteness, which strongly contrast with the surrounding normal tissue. No satisfactory explanation of this condition is at present forthcoming. The failure in the production of blood pigment seen in certain blood diseases probably deserves a distinct position.

Demonstration of Pigment in Tissues.—With the usual processes of fixation most pigments can be readily recognized within and between the cellular elements of the structures involved, but their identification is a more difficult task. The chemic and microchemic reactions of the various pigments are but poorly understood. In addition to the differentiating points previously indicated, the most important demonstration is that of iron. As before stated, hemosiderin contains iron; there are probably a number of pigments included under the name of hemosiderin merely from the fact that iron is present. The demonstration of the iron is usually accomplished as follows: Tissues that

[1] "Deut. med. Woch.," 1904, vol. xxx No. 24.

have been fixed in absolute alcohol are sectioned in the usual manner. Sections are treated for from one to two hours in a one per cent. aqueous solution of the ferrocyanid of potassium, and mounted in glycerin containing 0.5 per cent. hydrochloric acid. The pigment containing iron, not in the so-called concealed or masked form, will show the bright blue reaction. In order to secure the reaction with both ferric and ferrous salts it may be necessary to use a mixture of ferrocyanid and ferricyanid of potassium, each 0.5 to 1 gm. to 100 c.c. of water.

4. **Calcareous infiltration**[1] or **calcification** consists in the deposition in the tissues of salts of lime and magnesium; the lime salts are the phosphate, carbonate, chlorid, and fluorid; the magnesium salt is a phosphate.

The term **petrification or petrifaction** has been applied to deposits composed purely of magnesium and other than lime salts, while the term **calcification** has been restricted to lime salts. That so sharp a differentiation is advisable or even possible is, in the opinion of the writer, doubtful.

Causes.—Calcification is practically never a primary process; most frequently it is secondary to some destructive change in the cellular elements of the area involved: *e. g.*, local changes in nutrition, coagulation of albumin, slowing of the circulation, inflammation, necrosis, and chronic infections. Calcification is observed in processes intimately associated with certain forms of infection, as in the calcareous masses around tuberculous areas and in actinomycotic masses and in the fungus itself. Thomassen[2] has shown that, in animals immunized to the tubercle bacillus, the greater the immunity, the more marked the calcific deposit in areas containing the tubercle bacillus. The ultimate cause of the deposit of lime salts may be said to be unknown. The fact that it is more or less constantly associated with tissue death, or senescence, would indicate that disorganization or dissolution of proteid bodies favors the deposit; for this reason it has been held that the tissue elements in process of disorganization enter into chemic combination and retain within them the earthy salts, which, under normal conditions, escape or remain in the lymph or blood. In that form of tissue death, called fat necrosis, often associated with disease of the pancreas, the affected structures are promptly infiltrated by calcific matter. It is possible that the change results from a combination between fatty acids arising in the necrosed tissue and lime salts brought to the affected area by the circulating blood.

Morbid Anatomy.—The lime salts may form distinct concretions, as in tuberculous abscesses and tuberculous glands, or they may be diffused between or into the cellular elements of a tissue: *e. g.*, the cartilages of the ribs. This latter process is analogous to ossification observed in bone; calcification differs from ossification in that the former does not possess any distinct histologic structure.

Calcification is observed in "healed-in" infectious processes, or where attempts at "healing in" have been made; it also occurs in the

[1] Klotz, "Jour. of Exp. Med.," Nov. 25, 1906, March 26, 1906, and Aug. 1, 1906. Wells, "Jour. of Med. Research," Oct., 1907.

[2] "Rev. med. Vet.," 1903, vol. x, p. 5.

cartilages: *e. g.*, those of the ribs, and is frequently present in cicatricial tissues, particularly in those connected with the periosteum; it is seen in certain tumors,—*e. g.*, psammoma of the brain,—in thrombi, and in areas that have undergone hyaline, fatty, and possibly other degenerative and necrotic changes. The salts may be deposited both within and between the cells. Deposit within the cells is met with in the ganglion cells of senescence, but elsewhere the calcium salts are most commonly between the cells: that is, in the intercellular substance. Calcification following attempts at repair is observed secondary to inflammation of serous membranes, notably of the pleura and pericardium. It occurs as a sequence of inflammatory and degenerative processes in the blood-vessels, particularly the arteries, and is also seen around the cardiac orifices and in the older sclerotic areas in valve leaflets. A few remarkable cases of extensive calcareous infiltration of one or more of the internal organs have been recorded. The lungs may be sprinkled with calcific areas and ten to fifteen per cent. of the organ may be earthy matter. Similar **miliary calcification** is occasionally observed in the liver and spleen. Sometimes the tendon of the diaphragm is affected and large, calcareous plaques may be found in the mediastinum. In most of these cases, at autopsy, it is impossible to say exactly what was the primary lesion in which the lime salts were deposited. Tuberculosis at once suggests itself, but often no evidence in support of this view can be discovered. One of the remarkable instances of calcific deposit is that occasionally seen in the dead fetus of a ruptured ectopic gestation. In the course of years a fetus remaining in the abdominal cavity may be extensively infiltrated with lime salts, thereby producing a body spoken of as a **lithopedion.** Haultain[1] has recorded an instance in which a lithopedion was present in the abdominal cavity for forty-one years; the conformation of the fetus was so perfectly preserved that the projecting finger-nails could easily be identified. Calcification of the placenta is occasionally observed.

The *demonstration* of calcific deposits does not commonly require aid other than the gross examination. The deposits are usually sufficiently well marked to be readily recognized by palpation, and may be further shown by the occurrence of fracture on bending—a test particularly applicable to blood-vessels and valve leaflets. In sections, the calcific deposit is not uncommonly first discovered by the nicking of the microtome knife. When the deposit is scanty, the fine granules or grosser collections may be readily recognized under the microscope. The strong affinity of the salts for hematoxylin also constitutes an important test. The application of a five per cent. aqueous solution of hydrochloric or nitric acid leads to their disappearance, the carbonates effervescing as a result of the liberation of the carbon dioxid. The demonstration of lime salts may be further made by the addition of sulphuric acid, which leads to the formation of gypsum (sulphate of lime), which may be recognized as needle-like crystals.

Uric Acid Deposits.[2]—With gout is associated the abundant deposit

[1] "Jour. of Obstetrics of the British Empire," Oct., 1904.

[2] For recent interesting review of the various theories concerning gout, see "Practitioner," July, 1903, vol. lxxi, No. 1, pp. 1 to 106. Watson, "Lancet," Feb. 11, 1905, p. 347.

of uric acid and its salts, particularly in articular and para-articular structures, although the kidneys, skin, and fibrous tissues of the body are also likely to be involved. Wherever the deposit takes place there is usually a surrounding area of local necrosis, or at least marked degenerative changes. The cause of the deposits has not been definitely determined. We do not even know whether it is defective excretion, overproduction, or faulty oxidation. The deposition is frequently associated with local pain and inflammation. The statement commonly made that the deposits consist of sodium urate is not strictly true, as Roberts has satisfactorily demonstrated that they consist of sodium biurate, probably precipitated, in the tissues involved, from the quadriurate circulating in the blood. The uratic deposit in the cortex of the kidney is irregularly distributed, while in the medullary portion it follows the course of the straight vessels. The **tophi** in the cartilaginous external ear (the helix), the deposits in the eyelids, around the tendons, in the fibrous textures of the palms of the hands and plantar tissues, are composed of inflammatory, necrotic, and hyaline elements containing a varying amount of sodium biurate.

5. Glycogen Infiltration.[1]—Glycogen, like fat, is a normal constituent of liver tissue, arising from the metabolism of grape-sugar by the extraction of a molecule of water:

$$\underset{\text{Grape-sugar.}}{C_6H_{12}O_6} \;-\; \underset{\text{Water.}}{H_2O} \;=\; \underset{\text{Glycogen}}{C_6H_{10}O_5}$$

That it can also be produced from albumins there seems no reasonable doubt; but the uncertain composition of the proteid bodies makes the chemic change of albumin into glycogen an unsolved problem in physiologic chemistry. While produced normally in the organism, it is in diabetes that its most remarkable generation is observed. When we have solved the pathology of diabetes, the production of glycogen, and particularly its tissue infiltrations, may become apparent. It has a rather remarkable resemblance to amyloid material, and, still, that it is not the same can be easily established. It reacts with an aqueous solution of iodin very much as amyloid material, but does not give the blue with iodin and sulphuric acid; if treated with ptyalin or amylopsin, it quickly loses its iodin reaction; while amyloid is insoluble in water, glycogen is freely soluble. Glycogen is converted postmortem into grape-sugar. The extraction of glycogen from the liver is accomplished by dissolving it in an alkali and precipitating by alcohol. It is a white powder, freely soluble in water, giving the solution an opalescent tint.

Demonstration.—To demonstrate glycogen in the tissues, use anhydrous alcohol for fixation, infiltrate with celloidin, and harden in cedar oil and chloroform (p. 43). For staining, Barfurth advises a glycerin solution of iodin, and Ehrlich a syrupy solution of iodin in gum acacia. By either of these solutions it stains brown, like amyloid, but is differentiated by the insolubility of the last-named body. Fixa-

[1] For full bibliography see Chantemesse and Podwyssotsky, "Les Processus Généraux," 1901, pp. 242 to 246. Spezia, "Lancet," May 23, 1903, p. 1444. Best, "Deut. med. Woch.," 1902, No. 5, Vereins-Beil., p. 36. Helman, "Arch. internat. de Pharmacodyn. et de Therap.," vol. xii, fasc. ii and iv. Hulland, "Edinburgh Medico-Chirurgical Soc.," Feb. 3, 1904. Wolff, "Zeit. f. klin. Med.," Bd. li, p. 407. Driessen, "Centralbl. f. allg. Path.," Feb. 28, 1905, p. 129.

tion in absolute alcohol lessens its solubility but does not render it insoluble. On account of the readiness with which glycogen is dissolved it has been recommended to secure the iodin stain by exposing thin, undried cover-glass spreads to the vapor of iodin and mounting the film in a saturated glycerin or gum acacia solution of iodin.

As an infiltration, glycogen is found in the liver, epithelial cells of Henle's loops, in circulating leukocytes, and in pus-cells. It is present in the leukocytes in diabetes, and it is claimed that the diagnosis of diabetes can sometimes be made, before sugar appears in the urine, by the glycogen reaction of the white cells. The glycogenic reaction of leukocytes—**iodophilia**[1]—is seen in a number of infectious processes, particularly suppurative lesions, and is usually associated with leukocytosis. Many tumors contain glycogen. It is said to be more abundant in sarcoma than in carcinoma, and often forms a conspicuous element in tumors derived from adrenal cells (hypernephroma) and in neoplasms of the testicle and bone.

Morbid Anatomy.—Organs showing glycogenic infiltration resemble amyloid organs with the following exceptions: The specific gravity is low; there is not the bacony density; anemia and brittleness are less marked; the organs never attain the size sometimes seen in amyloid disease; and the difference given above in the chemic stain reactions. In cells from which the glycogen has been dissolved the protoplasm manifests a reticulated appearance, due to the cavities left by the removal of the infiltrating substance; this characteristic is particularly marked in the hepatic cell, but may also be seen in the renal epithelium and in neoplastic cells.

Cholesterin Infiltration.—There is much doubt as to this being an infiltration; in degenerative processes cholesterin is likely to be found, but gives no macroscopic evidence of its presence. Under the microscope it may be recognized as thin, rhombic plates with not very regular edges, and quite commonly each plate has a small square absent from one corner, appearing as though it had been cleanly cut out.[2] In addition to the degenerative processes already mentioned, cholesterin is found in the contents of cysts, and sometimes in inflammatory exudates and in atheromatous areas.

Hydropic Infiltration.—In edema the tissues involved are bathed in the fluid that distends the lymph-spaces, and the cells of the area may take up a varying amount of this fluid. By some this is considered an infiltration, and is spoken of as dropsical or hydropic infiltration. It is practically always associated with more or less degenerative change in the cells, and it has, therefore, seemed to the writer best to consider it with the degenerations. (See Hydropic Degeneration, also Edema.)

(B) DEGENERATION.

Degeneration[3] is characterized by retrograde changes in the protoplasm and nuclear structure of cells, and, though to a lesser degree, of acellular tissues. These alterations may be recognized by chemic

[1] See Diseases of the Blood, Part III, Chapter I.
[2] See illustration in chapter on the Microscopic Examination of Urine.
[3] For full bibliography see Chantemesse and Podwyssotsky, "Les Processus Généraux," 1901.

or microchemic methods and can often be seen in untreated cells. Infiltration may lead to degeneration, and degenerations may be accompanied by infiltrations; the processes, however, may be distinct. Notwithstanding the entity of each, an infiltration may be associated with a degeneration, the two tissue changes apparently going on side by side thus affording an obscure picture of both. In such complex processes, however, the degeneration is likely to be the lesion that is most detrimental, and while it may have been preceded by the infiltration, or the infiltration may have arisen after the inception of the degeneration still, the degenerative lesion will constitute the important pathologic phenomenon. Degenerations are also known as **metamorphoses.** Occasionally a degeneration is spoken of as a **necrobiosis;** this term is not, however, correct, as the latter condition implies molecular death and an organ or a cell may be degenerated and may not as yet be dead although ultimately the cell may perish. The degenerations are parenchymatous, fatty, hydropic, colloid, mucoid, hyaline, and corneous.

1. Parenchymatous degeneration, also known as **cloudy swelling, granular degeneration,** and **parenchymatous metamorphosis,** consists of a precipitate, within the cell protoplasm, of what seems to be albumin or other cell proteid, in a finely granular form. The nucleus of the cell is obscured, or even hidden, by minute granules, and, late in the process, may be destroyed; the perinuclear protoplasm contains an abundant granular precipitate; the cell outlines are indistinct, and the entire body may be disintegrated. It is probable that the process, if continued, terminates in a fatty degeneration, and that the granular bodies seen are eventually converted into oil. The cell may again be cleared up by the use of dilute acetic acid or a strong alkali. The nucleus often becomes visible, although the granular bodies may merely agminate and not disappear.

Causes.—High temperature; poisoning by carbonic, phosphoric, and arsenious acids, and by the salts of mercury, copper, antimony, etc.; intense or long-continued hyperemia, vascular stasis, and edema; inflamed mucous membranes usually manifest the change to a high degree; a similar process is seen in inflammation of muscle: *e. g.*, acute myocarditis; in acute yellow atrophy of the liver numbers of the cells are found granular and many of them fatty to a high degree; any malnutrition may simulate the condition, and many poorly nourished gland-cells, particularly in atrophic processes, show the change. Bacteria and their products, as well as other organic poisons,—the latter due to faulty metabolism or deficient excretion, or to combinations of both processes, —venoms, etc., are also causes. An examination of the causes just given discloses the fact that all are essentially toxic. Halliburton holds that the cell changes seen in high temperatures resemble necroses more than degenerations; their toxic origin can not be questioned.

Morbid Anatomy.—The affected organ is swollen, cloudy or opaque on its surface, appearing cooked, softer than normal, and, when the process is uncomplicated, there is evidence of anemia, but, as commonly seen, the amount of blood in the part is increased: *e. g.*, the cloudy swelling seen in the kidney may be the initial stage of inflammation, and the organ, under such circumstances, is usually distinctly hyperemic,

Termination.—If the cause be withdrawn early, it is probable that recovery of the cell may occur; if the cause continue to act, fatty

degeneration ensues, the cells are destroyed, and new cellular elements must be produced by the remaining structures, including the connective tissues.

Demonstration.—The alterations previously described in the gross organ usually enable one readily to recognize the condition. Examination of fresh cells obtained by scraping the surface of the tissue involved may offer confirmatory evidence, to be considered with the gross appearance. Too much confidence, however, can not be placed in the examination of detached cells. In such cells the granules clear up or agminate when treated with a one per cent. aqueous solution of acetic acid. They are not soluble in alcohol, ether, chloroform, or other agents that dissolve fat, nor are they blackened by osmic acid. Pieces of the organ under observation should be fixed in an osmic acid solution (see pp. 33 and 34), infiltrated with celloidin (paraffin is not applicable), and sectioned in the usual manner. The granules are not blackened by this process. Tissue fixed in corrosive sublimate or in Zenker's fluid (see pp. 34 and 35), sectioned, and stained with hematoxylin and eosin will commonly show the alterations to advantage. The intensity with which the granules take the acid anilin dyes is always notable

FIG. 138.—CLOUDY SWELLING OF THE EPITHELIAL LINING OF THE KIDNEY TUBULE.—(*Fütterer.*)

FIG 139.—GRANULAR DEGENERATION OF A MUSCLE-FIBER, LAST STAGE, NEARLY FATTY.—(*Schmaus.*)

FIG. 140.—CLOUDY SWELLING OF THE LIVER CELLS. × 250 diameters.—(*Schmaus.*)

2. **Fatty Degeneration or Fatty Metamorphosis.**[1]—This probably represents but a later stage of the preceding. In the cells, at this stage of the process, the granular bodies, before noted, are replaced by minute fat-like droplets; the nucleus is destroyed and can not be made to reappear; the cell is shrunken and not swollen; its outlines are apt to appear irregular, or evident cell dissolution may be manifest. The oil drops usually are smaller and do not run together as in fatty infiltration, although this difference is not constant nor characteristic. The compound granule cells in brain softening represent a type of fatty degener-

[1] Christian. "Jour. Med. Research," Aug., 1903, p 109. Rosenfeld, "Berl. klin. Woch.," 1904, Nos. 22 and 23. Orgler, "Virchow's Arch.," Bd. 176, No. 3. Fischler, "Virchow's Arch.," clxxiv, 2. Waldvogel, "Virchow's Arch.," 1904, Bd. clxxvii. Dietrich, "Münch. med. Woch.," Aug. 23, 1904, p. 1510. Christian, "Johns Hopkins Hosp. Bull.," Jan., 1905, p. 1. Shattock, "Jour. Path. and Bact.," Dec., 1903, p. 234. Arnold, "Münch. med. Woch.," Oct. 27, 1903, p. 1857. Ribbert, "Deut, med. Woch.," 1903, No. 44. Dietrich, "Arbeit. a. d. Path. Inst.," Tübingen, 1904, Bd. 5, H. 1. Torri, "Il Policlinico," Nov., 1902. Leick and Winckler, "Arch. f. exp. Path. u. Pharm.," vol. xlviii, p. 163.

ated cells. The cellular debris in the affected structures is usually abundant.

Causes.—(1) The causes already given for cloudy swelling; (2) anemia; (3) some of the forms of necrosis are accompanied by fatty degeneration: *e. g.*, caseation. Total or circumscribed fatty degeneration usually results from embolism, infection, or the noxious influence of bacterial toxins and allied agents. The relation of anesthesia, particularly by chloroform, to fatty degeneration is not fully explained. The studies of Guthrie[1] indicate that the prolonged administration of chloroform may cause fatty degeneration of organs, particularly the liver.

Morbid Anatomy.—As soon as the removal of fat by absorption begins, the organ diminishes in size, becomes soft, almost pultaceous, oily to the touch, and greases the knife with which it is cut. The affected part is paler than normal, yellow in color, markedly anemic, and may be the seat of interstitial or parenchymatous hemorrhage due to the degenerative processes involving the capillaries. The color of the organ may not be uniform, but mottled, as a result of the process being more active, or more marked, or at a later stage at some points. The color is also influenced by the amount of blood in the tissue and by the presence or absence of hemorrhage or of associated pigment. The conversion of the proteid matter into fat leads to a reduction in the specific gravity. The parenchymatous cells manifest the alteration earlier and in a more characteristic manner than the connective-tissue elements, which may escape. When the process is focal and marked, and in certain tissues,—as, for example, the central nervous system,—the softening may go on to complete liquefaction. (See Softening of the Brain.) Recent studies seem to indicate that the condition ordinarily called fatty degeneration is, in certain locations, a form of what has more recently been designated autolysis. Christian's study of the presence of fat in the resolving croupous pneumonia may be considered as corroborative of Flexner's views as to the method (autolysis) by which this disease normally undergoes resolution.

FIG. 141.—KIDNEY. EARLY STAGE OF FATTY DEGENERATION OF THE EPITHELIUM OF THE CONVOLUTED TUBES; FROM A CASE OF PERNICIOUS ANEMIA.

Osmic acid preparation. Parts of three convoluted tubes and one collecting tube are shown. The epithelium of two of the convoluted tubes, near the center of the drawing, is the seat of advanced granular and less marked fatty change. The protoplasm is granular and fragmenting and contains droplets of fat that have been blackened by the osmic acid.

[1] "Lancet," July 4, 1903, p. 10.

Fatty degeneration affects particularly epithelial surfaces and glandular viscera, muscles, nerves, and blood-vessels; occasionally it is observed in the brain, and there constitutes a variety of softening. In certain localities the process is apparently physiologic: for example, the production of fat by degeneration of the central cells of the acini, in the mammary gland, leading to the formation of milk, and the fatty change seen in the uterus after labor. (See Fatty Degeneration of the Heart, Blood-vessels, Liver, etc., Part VII.)

Demonstration.—The highly refractive oil globules can usually be recognized under the microscope. In fresh tissues the affected cells are not cleared up by acetic acid; they are blackened by osmic acid; the black or brownish-black granules produced by treating fat with osmic acid are not soluble in alcohol during the subsequent dehydration, but

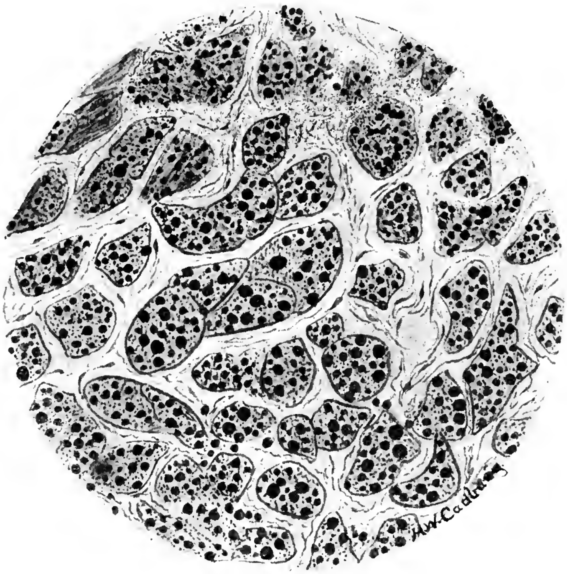


FIG. 142.—HEART, TRANSVERSE AND OBLIQUE SECTIONS OF MUSCLE-FIBERS, SHOWING FATTY DEGENERATION Osmic preparation, from case of pernicious anemia.

may undergo partial solution during the process of clearing for paraffin infiltration, and particularly when subjected to the action of fat solvents, such as chloroform, turpentine, xylol, etc. For the demonstration in sections fixation in alcohol is not applicable. Tissues should be fixed in one of the osmic acid solutions (see pp. 33 and 34), dehydrated, infiltrated with celloidin, and sectioned. The fat globules will be blackened by this method. Blocks of tissue may be fixed in Müller's fluid (see p. 31) or in Orth's fluid (see p. 31) or in a ten per cent. solution of formaldehyd for a week or ten days. The tissue is then transferred to Marchi's fluid, which consists of:

Müller's fluid,	2 parts.
One per cent. aqueous solution of osmic acid,	1 part.

The tissue is permitted to remain in this solution for a week or ten days. For successful treatment the blocks of tissue should be very small—not over two to five millimeters in thickness. Embedding in celloidin is permissible. After cutting, the sections are cleared in cedar oil and mounted in balsam without staining. The fat globules will be black or brownish-black. When desired, sections may be stained in the usual manner, which will permit an examination of the nuclei and of the associated structures to advantage (Figs. 142 and 143). Paraffin infiltration does not yield so satisfactory or trustworthy results as celloidin, as the preliminary clearing agents are liable to extract a part of the fat.

Scharlach R, Sudan III, and Fettponceau are stains useful for the demonstration of fat in cells or in tissue. Sudan III is commonly employed. A saturated solution of the dye in seventy per cent. alcohol is the most convenient strength. The suspected fluid and cells are spread upon a cover-glass and fixed in formalin vapor for five or ten minutes. The film is then washed in water, rapidly rinsed with seventy per cent. alcohol, and flooded with the alcoholic solution of the stain. Afer ten minutes the dye is quickly washed off with seventy per cent. alcohol, dried and mounted in glycerin, glycerin-jelly, or Farrant's medium.[1] Scrapings from the incised surfaces of organs, or small fragments torn to pieces by needles, may be treated in the same way. For the demonstration of fat in fresh tissues the specimen may be fixed in formalin, Orth's fluid, or Zenker's solution, and sectioned with a freezing microtome; sections are stained twelve to twenty-four hours in hematoxylin diluted with water, followed by frequent changes of water until the color is no longer extracted. The sections are then placed in the alcoholic solution of Sudan III for fifteen to twenty minutes, rapidly washed in seventy per cent. alcohol, transferred to water, and mounted in glycerin, glycerin-jelly, or Farrant's medium. For the demonstration of fat in tube casts the urine should be sedimented and the deposit washed in several changes of water. A drop of the fluid containing the casts is mixed with an equal volume of seventy per cent. alcohol and a drop of the alcoholic solution of the stain added. In this fluid, examined under the microscope, the fat can easily be identified within the epithelial cells or casts. Sudan III stains the larger fat droplets a rather deep scarlet; the smaller particles are golden yellow. The reaction seems to be quite selective.[2]

3. **Hydropic degeneration,** or **hydropic metamorphosis (cellular dropsy, cellular vacuolization),** is practically an intracellular edema. The affected cells are very much larger than normal, and contain many so-called vacuoles, usually in the perinuclear protoplasm, although the nucleus may be involved. The evident cell damage is less than in parenchymatous degeneration, but may be most marked when the two processes are associated, as is not uncommonly the case.

Causes.—In many instances the process is clearly toxic. Exactly how poisons induce this form of change can not be stated. It is seen particularly in edema, inflammation, infectious processes, and degenera-

[1] Farrant's medium consists of glycerin, gum arabic, arsenious acid, and water. It is difficult to prepare and had best be purchased from a dealer in supplies. In some climates it forms a satisfactory medium for permanent mounts.

[2] For further review of methods see Fischler, "Centralbl. f. allg Path.," Nov. 30, 1904, p. 913. Stransky, "Neurolog. Centralbl.," July 16, 1903, p. 658. Meyer, "Centralbl. f. Nervenheil. u. Psych.," 1903, vol. xiv, No. 7.

tive lesions in general when affecting the large ganglion cells of the central nervous system.

Hydropic degeneration is frequently observed in the cells of pithelial surfaces, particularly the mucous membranes, glandular viscera in inflammation and edema, edema of the muscular tissues in which many fibers are swollen and, on transverse section, show extensive central vacuolation. The morbid anatomy is practically that of edema, but hydropic degeneration is often present when no gross alteration is manifest.

Demonstration.—No specific method has as yet been devised for the demonstration of this process. Rapid and powerful fixatives are demanded in order to prevent the cell from emptying itself of the fluids before fixation is completed. Probably the best results are obtained by fixing small pieces of the tissue in corrosive sublimate (see p. 34), followed by hematoxylin and eosin staining.

4. **Colloid degeneration,** or **colloid metamorphosis,** is a process by which cellular protoplasm is converted into a homogeneous, gelatinous structureless substance called *colloid.* The exact cause of this change is not known; it occurs in connection with epithelial cells, to which it is practically restricted. It is, therefore, a common phenomenon in glandular structures where exit is prevented by occlusion of the duct; it is seen in the kidney and in ovarian cysts, it occurs in goiter and in cancerous masses. The constancy with which it is found in the thyroid gland has led many observers to believe that it is a normal constituent of that organ, and, when greatly increased in amount, the condition is spoken of as colloid goiter. The exact chemic nature of the material has not been definitely settled; it is not precipitated by alcohol or acetic acid, it is not readily soluble in water, and is not rendered opaque by chromic acid.

Macroscopically, the material is gelatinous, stringy or ropy, and is usually colorless, but may be slightly bluish or yellow.

Microscopically, it will occasionally be observed to be arranged in concentric masses. It does not stain well with the anilin dyes, but stains with carmin.

Colloid degeneration of muscle has been described by Zenker, and is closely allied to the hyaline degeneration, which he also describes. Colloid material is found in some cancers, particularly in those of the alimentary canal; it is also found in cysts possessing an epithelial wall. Colloid transformation occurs in the cerebral vessels, where, according to Mallory, it is particularly subject to subsequent calcareous change. (For demonstration and differentiation from amyloid, mucoid, and hyaline material see paragraph following Hyaline Degeneration.)

5. **Myxomatous degeneration,** also known as **mucoid degeneration** or **myxomatous metamorphosis.**[1] Myxomatous material is normally found in Wharton's jelly and in the vitreous humor. The process terminates in the formation of a semifluid, hyaline body containing a varying quantity of mucin. A further study of mucin has led to the recognition of the fact that what was originally considered to be a chemic entity is now found to occur under a number of conditions and in more than one form. In epithelial structures the mucin exists in the mucus elaborated within certain of the cells, which assume, as a result of the accumulation in their interior, a goblet form, and hence are called *goblet cells.* The free end of the cell opens and the accumulated contents flow out, the cell

[1] Chantemesse and Podwyssotsky, "Les Processus Généraux," 1901.

returns to its normal shape and resumes the manufacture of mucus. In other instances the cell is actually shed, undergoes dissolution, and liberates the elaborated product. During inflammatory processes in epithelial surfaces the quantity of mucus produced is notably increased. The production of mucoid material is not, however, restricted to the epithelial tissue, but is intimately associated with the connective tissues, and arises from the transformation of the cell, or, more frequently, and probably more truly, of the intercellular substance into a jelly-like material containing mucin. Chemically, the material seems to be made up of complex albuminous compounds in which mucin is abundantly present. The affected area is gelatinous and trembling, almost perfectly clear, and colorless.

In **myxedema** the subcutaneous and, to a certain extent, other tissues are the seat of marked swelling, and between the fibrils is intercalated a somewhat hyaline, almost homogeneous substance, that Ord has shown contains a mucin. Apparently the alteration is not identical with some other forms of myxomatous degeneration, but the resulting product possesses a number of the characters seen in tissues affected by mucoid metamorphosis. Myxedematous tissues are solid, do not pit on pressure, and when incised yield practically no serum. The vascularity is greatly reduced and the nutrition proportionately altered. (See Diseases of the Thyroid Gland.)

Microscopically, mucoid material is quite homogeneous, and not uncommonly contains large multipolar cells with long, branching filaments. These form a reticulum, which supports the gelatinous material and maintains conformation of the affected structure; it is not arranged in concentric masses, like colloid material. Mucoid material is precipitated by alcohol and acetic acid, and is best fixed by corrosive sublimate. It will absorb considerable water, which causes it to swell; it does not, however, undergo solution. It is dissolved by neutral salt solutions and by alkalies, even in comparatively weak solutions. (For further remarks on demonstration see paragraph following Hyaline Degeneration.)

As before indicated, *mucoid degeneration* occurs in both connective and epithelial tissues; it is present in certain connective-tissue tumors, most commonly in myxoma and lipoma, occasionally in sarcoma or chondroma, and rarely in carcinoma.

6. Hyaline degeneration, also known as **vitreous** or **glassy degeneration** or **hyaline metamorphosis.** The exact nature of the material produced, and the method by which it is elaborated, have not been worked out; the body seems closely related to colloid material, but is firmer, more fragile, and arises in a different class of tissues; it is most commonly found in the lymphatic glands and blood-vessels, including the capillaries, around which it may form a distinct mantle; it is occasionally observed just outside the intima of the blood-vessels and around the capillaries, thus closely resembling amyloid material. It does not, however, give the amyloid reaction. Hyaline material is occasionally observed in the brain, in the stroma of epithelial tumors, and in the dendritic filaments of papilloma of the bladder and other mucous surfaces. The degenerative change observed in the muscles in typhoid fever, particularly in the abdominal recti and the muscles of the upper portion of the thigh, has been variously placed. By some it is regarded as a

special degenerative change restricted to muscle; by others it is grouped with the hyaline degenerations; while still others regard the change as a form of coagulation necrosis.

Amyloid, colloid, mucoid, and hyaline materials are closely allied bodies. Thoma, von Recklinghausen, and Graham regard each as representing but different stages in the evolution of the same body. Lardacein apparently presents sufficiently distinct reactions to entitle it to be considered alone. That the remaining conditions are separable by methods at present at our disposal seems doubtful. Differentiation by stain reaction—the only method at present available—is not fully characteristic or always satisfactory. Hyaline and colloid materials seem to select acid stains, while mucoid is commonly best stained by basic dyes. Pianese differentiates these materials by fixing small pieces of tissue (2 mm. thick) in a mixture composed of 15 c.c. of a 1 per cent. aqueous solution of chlorid of platinum and sodium; 5 c.c. of a 0.25 per cent. aqueous solution of chromic acid; 5 c.c. of a 2 per cent. aqueous solution of osmic acid; and one drop of chemically pure formic acid. After thirty-six hours' fixation the tissues are washed in flowing water and transferred to eighty per cent. alcohol. Sections are stained for half an hour in the following solution:

Martius yellow,	0.01	gm.
Acid fuchsin,	0.1	gm.
Malachite green,	0.5	gm.
Distilled water,	150	c.c.
Alcohol (96 per cent.),	50	c.c.

After staining, wash in absolute alcohol, treat with xylol, and mount in xylol balsam. By this method mucin is stained sky-blue; hyaline, brick-red; colloid, bright green.

Corneous degeneration, keratoid metamorphosis, keratohyaline degeneration, keratosis, or **hyperkapatosis,** are a few of the many names given to a condition characterized by excessive cornification of epithelium. It is an exaggeration of the normal process by which the epithelium of the Malpighian layer of the skin is transformed into the corneous stratum. The chemic product resulting from this change is called *keratin.* This substance is insoluble in cold or boiling water, in dilute acids, and in alkaline carbonates; it resists digestion and putrefaction and is converted into alkaline albuminates and hemialbumose by a concenerated caustic alkali. When stained by the method of Gram, it is found to contain numerous small granules (keratinic granulations of Ernst) which take the dye intensely. The formation of keratohyaline is practically always most advanced in epithelial cells farthest from the source of nutrition.

Pathologic keratinization is seen particularly in ichthyosis, keratosis, and in lingual, buccal, and vaginal psoriasis. A large part of the typical cell nests of squamous epithelioma, when fully developed, are composed of keratinized epithelial cells. The epithelium covering papillomas and the hardened superficial layers of ordinary corns are composed of keratinized epithelium. Cutaneous horns usually consist of more or less perfectly laminated epithelial cells that have undergone this change.[1]

[1] For fuller description of the process see Chantemesse and Podwyssotsky, "Les Processus Généraux," 1901, p. 154, bibliography, p. 207.

CHAPTER IX.

NECROSIS.

Necrosis is the local death of a part, as distinguished from somatic death. When necrosis of any structure results from trauma applied directly to the tissue, it is known as **direct necrosis**; when the change is dependent upon causes applied through the circulation, innervation, or degenerative processes, it is called **indirect necrosis.**

Causes.—Anything that destroys the vitality, *e. g.*, burns, scalds, and chemic destruction or injury sufficient to interfere with nutrition. The influence of trauma need but be mentioned, as the extensive laceration of the cells, with the associated disturbances of circulation, both hemic and lymphatic, makes cellular death inevitable. The method by which poisons produce necroses is not always apparent. Of the many toxic substances endowed with the property now under consideration, certain of them are inorganic, such as mercury, phosporus, copper, arsenic, etc.; others are organized bodies, which may be again subdivided into at least three groups: (1) Vegetable poisons (from the higher forms of vegetable life many bodies might be mentioned, *e. g.*, oil of mustard, abrin, ricin, etc.), bacteria, and bacterial poisons, such as the toxin of the Bacillus diphtheriæ; (2) poisons belonging to the animal kingdom, such as those elaborated by poisonous reptiles; (3) certain toxic bodies produced by the tissues themselves. As an example of the noxious influence of the last group, it is but necessary to refer to the extensive hepatic necroses that occur in uremia, and in that particular form of intoxication known as eclampsia.[1] The association of inflammation with necrosis may be either primary or secondary: that is to say, necrotic processes may give rise to, or be followed by, inflammation; on the other hand, inflammation is always associated with a varying degree of necrosis. Obstruction to the circulation—arrest of the arterial influx, capillary flow, or of the venous exit—may cause necrosis; lymphatic obstruction may have practically the same effect; capillary stasis, thrombosis, or rhexis is usually followed by necrosis of the tissues involved.

As nutrition is, in part, governed by the trophic nerves, it is held that certain necrotic changes result from lesions of these nerves or the central nervous system acting through them. Such necrotic processes are known as **neuropathic necroses.**

The cause of any given necrotic process may have been complex, more than one element, and in some instances many factors, entering into its formation. In the weak and debilitated, after fevers, in malignant diseases, and, in certain instances, following profound shock, necrotic changes are induced by injuries and other causes that, in the physically strong, would give rise to but little or even no important

[1] See page 80.

tissue alteration. As examples of necrosis arising in part through such influences, **marasmic** and **senile necroses** may be mentioned.

Results.—The tissue involved may undergo (1) regeneration or the nearest approach thereto, repair; (2) absorption, more or less complete; (3) retention in some form or another; or (4) it may be discharged. The possibility of associated or subsequent inflammation is not to be forgotten.

1. Regeneration and Repair.—In some instances the necrosed elements are thrown off or absorbed, and adjacent cells or embryonic constituents of the tissues involved may produce new tissue structurally and physiologically identical with that lost, in which case the lost structures are said to be regenerated. More frequently, absorption of the liquefied elements occurs, and repair proceeds to the formation of cicatricial tissue, which remains as a scar occupying the area of the original lesion.

2. Absorption is possible only when the liquefaction can be complete and when bacteria do not gain access; such absorption is typified in bruises in which the extruded blood-cells are, in time, completely removed.

3. Retention.—The entire mass may be retained, or partial absorption and reparative changes may leave but a part; thus, if an embolus cut off the blood-supply in a branch of the renal artery, the area involved—say, a part of a pyramid—dies; after certain degenerative processes, leukocytes and fixed connective-tissue cells wander in and convert the mass into embryonic tissue, from which granulation tissue is evolved and eventually cicatricial tissue (organization). Only a part of the involved tissue may be retained, and this may be much altered: *e. g.*, in the blood cyst, or hematoma, a fibrous capsule may be formed surrounding the escaped blood. Some of the fluid contents may be removed by the absorbents, and the remaining solid material, derived from the clot and cellular elements, becomes permanent, or degenerative changes may convert the mass into a cyst.

4. Discharge.—The necrotic mass may be thrown off, as in gangrene, or it may be slowly disintegrated, as in suppuration, ulceration, and caries.

Forms of Necrosis.—Liquefaction necrosis, coagulation necrosis, fat necrosis, cheesy necrosis, sphacelation *en masse* or gangrene.

1. Liquefaction or **colliquative necrosis** arises as the result of infection, particularly by pyogenic organisms, and is induced by irritants that are not sufficiently active to produce coagulation necrosis. It differs from coagulation necrosis in the absence of coagulation; there is the same infiltration of the tissues with fluid, but coagulation does not occur. Pus production resulting from infection represents a type of liquefaction necrosis, in that bacterial products, and possibly other bodies, liquefy the intercellular substance retaining the leukocytes and other cellular elements, and thus convert the area involved into a liquid. Liquefaction necrosis is sometimes seen to follow coagulation necrosis, and coagulation of previously liquefied areas is occasionally observed. It has been shown that tissues normally contain, or may produce, substances possessing the power of liquefying structural elements. As a result of such liquefaction (autolysis) absorption is rendered possible.

Morbid Anatomy.—The gross appearance depends largely upon the

tissue involved, and, to a certain extent, upon the cause. The increased amount of fluid in the part may make it softer than normal—indeed, it may fluctuate; in other situations the associated increased tension gives rise to apparent induration, which disappears on incision or puncture permitting the escape of some of the fluid. In the absence of coloring-matters, including blood pigment or its derivatives, the color is lighter than the normal. Concurrent fatty degeneration leads to the presence of minute oil drops,—an emulsion,—which may give the softened area a greasy appearance. Histologically, the structural elements pass through hydropic, fatty, and other degenerative processes, and, finally, may no longer contain a single structurally normal constituent. Absorption, retention in part or as a whole, and discharge are possible terminations; repair, more or less complete, occasionally occurs, but regeneration is extremely rare, if even possible.

The results of liquefaction necrosis are seen in the fluid exudate in burns, vesicles, etc., and in softening of the central nervous system; secondary liquefaction of coagulated exudates occurs in croupous pneumonia, blood-clots and thrombi.

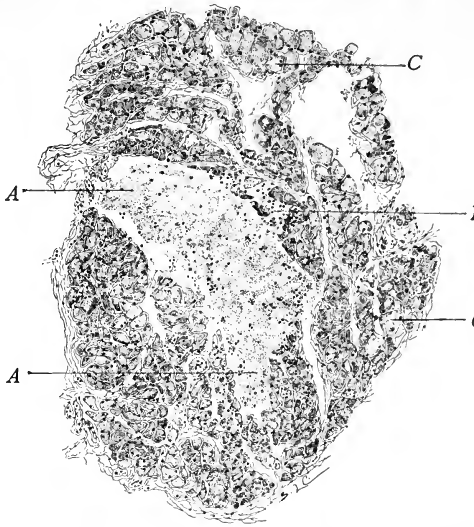


Fig. 143.—Intercostal Muscle, Transverse Section, from a Case of Epipneumonic Pleurisy, showing Area of Coagulation Necrosis.

Tissue fixed in Zenker's fluid; hematoxylin and eosin stain. *A*, *A*. Necrotic area in some portions of which the shadowy outlines of muscle-fibers may still be distinguished. *B*. A few mononuclear leukocytes, mostly of the lymphoid type, aggregated on the margin of the necrotic area. *C*, *C*. Fragmenting vacuolated fibers (hydropic degeneration), of which several can be seen in the field.

2. **Coagulation necrosis** occurs as a part or sequence of infection; as a result of embolism or capillary plugging. In areas of interstitial hemorrhage and in blood-clots, the mass undergoes coagulation necrosis. Usually the affected tissues are matted together with fibrin, which entangles whatever cellular elements may be present; occasionally fibrin is absent or not demonstrable. When occurring in superficial structures, as on or in the mucosa in diphtheria, the fibrin found may be hyaline or homogeneous, fibrillar, or, in some instances, granular. The view at one time held that fibrin of the blood was essential to the process, is now admitted to be incorrect, as lymph containing fibrinogen may induce the change. Zenker's degeneration of muscle is, by some, held to be a form of coagulation necrosis. As an example of coagulation necrosis following infection may be mentioned its occurrence in diphtheria, tuberculosis, typhoid fever, and allied conditions. It does not seem that bacteria at the point of necrosis are necessary, but that the

process may be engendered by the activity of bacterial products; that it may be due to chemic agents circulating in the blood is shown by the intravascular injection of *abrin* or *ricin*, which is followed by coagulation necrosis in different organs. After the tissues are matted together by fibrin, fragmentation of the nuclei (karyolysis) and more or less complete dissolution of the cells occur. In active inflammatory processes, or in the tissues immediately adjacent, coagulation necrosis is nearly always present. It not uncommonly precedes caseation, and may be present in the neighborhood of caseous areas.

Morbid Anatomy.—Early in the process the tissues become very much firmer than normal; not uncommonly the area can be recognized by palpation, even when situated some distance beneath the surface. Upon incision the freshly cut surface may resemble the opaque, glassy appearance of cloudy swelling. Later, softening not uncommonly occurs, which may progress to liquefaction. In the absence of blood or of blood coloring-matter or its derivatives, the area is lighter than normal. Histologically, the cell outlines soon disappear and the normal microchemic reactions are altered. The nuclei at first stain very faintly with the basic dyes, but later not at all, and just before complete dissolution of the cell its entire structure may take the acid dye only. Occasionally, however, even late in the process, fragments of nuclear chromatin may be irregularly disseminated through the area, and may show as irregular granules taking the basic dye in the midst of a fine granular mass that selects the acid stain. By suitable methods the presence of fibrin can be shown at some stage in the development of the process.

For the purpose of demonstrating the presence of this body Weigert's fibrin stain is recommended. Sections of alcohol-hardened tissue are fastened to the slide by an approved method. The subsequent staining is conducted as follows:

Anilin gentian-violet solution[1] two to ten minutes; rinse in normal salt solution;[2] apply solution of Lugol (iodin, 4 parts; iodid of potassium, 6 parts; water, 100 parts); rinse in water; blot with filter-paper; differentiate in a mixture composed of anilin 2 parts, xylol 1 part; complete differentiation in xylol, which should be applied and removed at least three times; when the section becomes fully cleared, mount in balsam. *Dehydration and differentiation with alcohol are not permissible.*

Termination.—Discharge may occur as in pseudomembranous formation. (See Pseudomembranous Inflammation of Mucous Membranes.) Liquefaction, absorption, retention, or suppuration usually occurs. More or less absorption, followed by repair, is not infrequent. As in liquefaction necrosis, regeneration of the destroyed tissue is not common. On the surface of the mucous membranes, however, the destroyed cellular elements are not infrequently regenerated.

Coagulation necrosis is possible wherever embolism may occur, and in all forms of capillary stasis; it involves the cells of epithelial surfaces and glands made up largely of epithelium, such as the liver; the same condition has been observed in the connective tissues, muscles, and fat. Halliburton[3] states that the cell change seen in

[1] For formula, see chapter on Bacteriologic Technic.
[2] Sodium chlorid, 0.75 per cent. in water.
[3] "Lancet," June 22, 1901.

the brain substance and thought to depend upon high temperature has been recognized by Marinesco as a form of coagulation necrosis. Anglade[1] holds that in all cases cerebral softening is a necrosis, pure and simple; it may primarily be coagulative, but rapidly proceeds to liquefaction.

3. Fat Necrosis.[2]—Whether this deserves a distinct position among the necroses is not fully determined. It is most constantly associated with hemorrhagic pancreatitis, in which condition it occurs in the pancreas, peripancreatic fat, and in the fat of the abdominal wall. It has been found in other conditions, and with no discoverable lesion of the

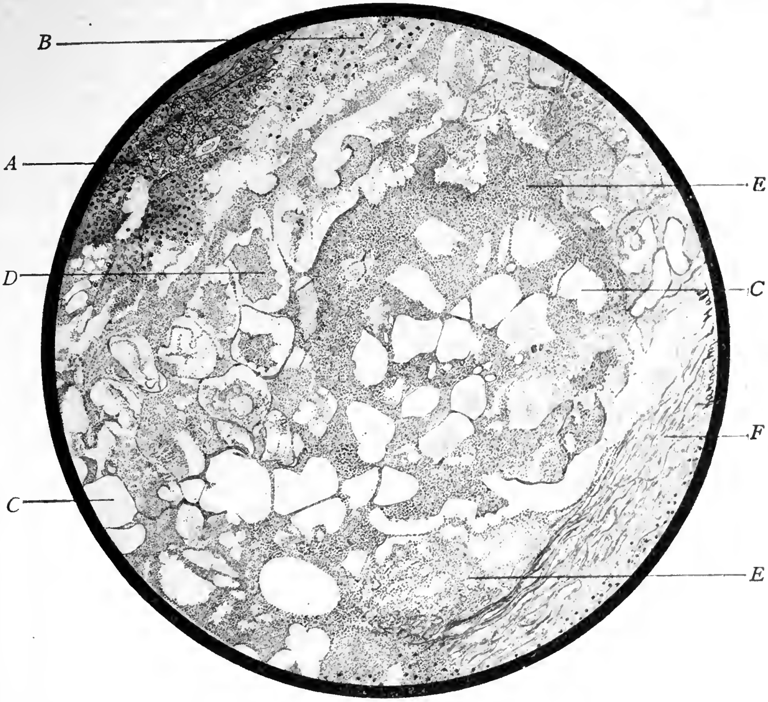


Fig. 144.—Fat Necrosis Accompanying Acute Hemorrhagic Pancreatitis.

The area shown in the illustration is from just beneath the investing fibrous tissue of the pancreas. *A*. Margin of area of hemorrhage. *B*. Fragmented nuclei in area of necrosis. *C*, *C*. Fat cells that have escaped destruction. Many other unaffected or but slightly changed fat cells are present. *D*. Fat cell in which the necrosis is incomplete. *E*, *E*. Areas in which the necrosis is practically complete. *F*. Part of peripancreatic fibrous tissue.

pancreas. The areas of fat necrosis vary in size from one or two millimeters to five centimeters, are usually spheroid or ovoid in outline, are white, yellowish-white, or gray, and resemble, in a way, disseminated

[1] "Soc. de Biol.," March 4, 1905.

[2] Williams, "The Morbid Anatomy and Etiology of Fat-Necrosis," Buffalo, 1900. Truhart, "Pankreaspathologie," Teil I; "Multiple abdominale Fettgewebsnekrose," Wiesbaden, 1902. Ponfick, "Beitr. zur Lehre v. der Fettgewebs-Nekrose," 1902. Guthrie, "Jour. Amer. Med. Assoc.," July 4, 1903, p. 7. Wells, "Jour. Med. Research," 1903, vol. ix, No. 1. Hart, "Münch. med. Woch.," Jan. 12, 1904. Haffner, "Münch. med. Woch.," Aug. 16, 1904, p. 1473. Hewlett, "Jour. Med. Research," May, 1904, p. 377.

neoplasms or tubercles. Histologically the oil content of the fat cells is converted into a finely granular debris which no longer takes osmic acid; nuclear structures in the affected area are fragmented. In the earlier stages leukocytes are absent, and, when infection does not occur, play no important part in the process. In time the necrotic tissue may be infiltrated by lime salts; this infiltration is further explained if we accept the statement of Langerhans that the necrotic areas consist of a combination of the fatty acids with lime salts. Sometimes areas are softened, but later, as a result of the calcific matter present, they become gritty. The presence of steapsin, the fat ferment of the pancreas, has led to the belief that this body is the essential factor. Some hold that the process depends upon bacteria or bacterial products, while others believe that it is brought about by trophic influences. Recent clinical and experimental evidence indicates that the change in the fat is due to the activity of the pancreatic ferments, and that the older theories can be discarded.

4. **Cheesy necrosis,** or **caseation,** frequently begins as a coagulation or liquefaction necrosis, followed by a fatty degeneration of the cellular elements, and the conversion of the mass into a liquid or semifluid material resembling cheese. In some cases the fluid is taken up by the lymphatics, giving rise to *dry caseation,* such as is seen in old tuberculous abscesses in which the substances resulting from liquefaction necrosis have been absorbed, leaving nothing but the cellular detritus. Caseation is not always dependent upon the removal of the fluids and the retention of the solid particles, as is shown by the fact that many caseous areas undergo no diminution in size at any period in their evolution. This is partly explained by the occurrence of cell migration into the necrotic area, the newly arriving cells themselves undergoing necrosis and their solid constituents remaining. The entrance of cells and fluids, as well as the absorption of the latter, account for the nodules retaining approximately their original size. In addition to the detritus, arising from disintegration of the normal elements present, and the necrotic cells, caseous nodules may contain bacteria. The organism most frequently present is the tubercle bacillus, which may be at times demonstrated in caseous nodules that are evidently old. Recently formed caseous areas are not uncommonly surrounded by a zone of inflammation. Older nodules may, from causes not well understood, show recrudescence of the original process. Schmoll[1] has shown that caseous products of tuberculosis consist chiefly of coagulated proteid the elementary composition of which resembles albumin, like which it may be converted into albumoses and peptone.

Once the caseous mass is thoroughly encapsulated, it becomes permanent; the capsule frequently calcifies, and lime salts may be infiltrated into the cheesy material, converting it into a stone-like structure. The condition can not be properly said to be a cure, but only a quiescent stage, likely at any time to be followed by recrudescence of the original exciting cause.

Causes.—The process arises almost exclusively in connection with tuberculosis, but is occasionally seen in other chronic infections; in some instances small nontuberculous abscesses may caseate. Caseation is sometimes seen in serous cavities: *e. g.*, pericardium or pleura. Rarely

[1] "Deut. Arch. f. klin. Med.," 1905, lxxxi, p. 163.

the retention of mucoid materials, as in the Fallopian tubes, may be followed by inspissation and caseation.

5. Sphacelation en masse, or Gangrene.—This process is also known as *mortification*. A surgical term, *necrosis*, is applied to death of bone *en masse*. Gangrene or mortification is the death of any tissue, followed by putrefaction, while attached to the living body.

Varieties.—(*a*) *Moist gangrene*, which is further divided into (*1*) *circumscribed* and (*2*) *spreading;* (*b*) *dry gangrene;* (*c*) *hospital gangrene.*

(*a*) **Moist gangrene** may arise from disturbance of the blood-supply—arrest of arterial influx, capillary flow, or venous exit. Gangrene

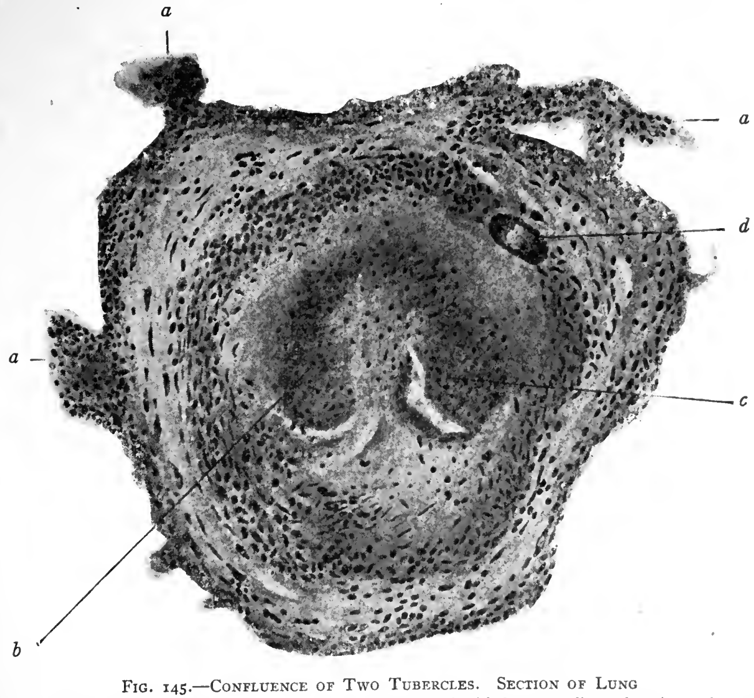


FIG. 145.—CONFLUENCE OF TWO TUBERCLES. SECTION OF LUNG

Hardened in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin, and mounted in balsam. The mass has originated in the vesicular wall, parts of which can be seen at *a*, *a*, *a*, running off to surround adjacent air vesicles; *b* and *c* have been two distinct tubercles, which are now beginning to show caseation. Around the caseous area is a zone of lymphoid cells in which, at *d*, is a solitary giant cell. Such eccentrically placed giant cells are not infrequent. The vesicular walls, which leave the tubercle mass at *a* *a*, *a*, show considerable thickening (⅛-inch objective, ½-inch ocular).

may result from edema; when due to injury, it is known as *traumatic gangrene*; when caused by inflammation, it is called *inflammatory gangrene*. The inflammatory processes arresting capillary circulation, coagulation necrosis occurs, followed by gangrene. The cutting-off of the blood-supply may result from occlusion of the artery by an embolus or thrombus, or a similar obstruction of a vein. Continuous pressure upon an area by progressive lessen ng of the blood-supply leads to softening, and is followed by infection giving rise to gangrene. Destruction of tissue vitality by injury, whether traumatic, chemic,

or thermic, leads to gangrene if putrefaction occur. Eichhorst[1] has been able to collect 166 cases of gangrene associated with or following infectious disease. In 65 cases examined at autopsy thrombosed arterial trunks were found. Ricketts collates 134 cases of gangrene in typhoid fever; varicella gangrænosa also belongs with this group. The gangrene occurring in infectious diseases commonly involves a number of areas (*multiple gangrene*) and sometimes affects the same parts on the two sides of the body (*symmetric gangrene*). Thayer's studies of arteritis accompanying infectious diseases, particularly typhoid, clearly indicate the character of the lesion (thromboarteritis or thrombophlebitis) upon which the gangrene depends.

Chronic thrombosing or obliterative endarteritis[2] sometimes terminates in gangrene. The condition is occasionally seen in the young, and differs in a number of respects from arteriosclerotic gangrene occurring later in life (see Arteriosclerosis). The gangrene produced by obliterative endarteritis involves particularly the extremities; in the case reported by Morgan all the limbs were affected and one hand and both legs were amputated.

Gangrene in all its forms represents death of the tissue involved plus infection. In the absence of infection mummification, or drying without putrefaction, occurs. Such a condition is rarely, if ever seen, certainly not in masses of any considerable size. The odor of dry gangrene is significant of the presence of bacteria. In **spreading gangrene** a violent infection occurs, extending by the lymphatics, and with such rapidity as to preclude arrest by the resources of the tissues involved. In **circumscribed gangrene** the process is limited by the protective influence of the body juices and cells and extends no farther than the line of demarcation described below; in spreading gangrene no line of demarcation is formed. The infectious processes associated with gangrene are not fully understood. There is, however, a form of spreading gangrene—**malignant edema,** due to a bacillus—that has been thoroughly studied. (See Malignant Edema, p. 136.)

Noma, or **cancrum oris,** is a gangrenous process that attacks the mucosa of the mouth, lips, and adjacent structures. (See Diseases of the Alimentary Canal, Part III.) A similar if not identical process has been observed in the external genitals, particularly in the female. The affection sometimes manifests an epidemic tendency, especially where large numbers of children are congregated. Blumer and MacFarlane[3] report an epidemic of 16 cases. Of the 133 cases collated by Krahn, 55 followed measles. The disease is practically restricted to childhood, but occasionally is seen in debilitated adults, particularly consumptives, and those recovering from such

[1] "Deut. Arch. f. klin. Med.," Bd. lxx, H. 5 and 6. See also Keen, "Surgical Complications and Sequelæ of Typhoid Fever," 1898. Edwards, "Archives of Pediatrics," Aug., 1903. Ricketts, "Cincinnati Lancet-Clinic," Dec. 5, 1903. Auché and Laterrille, "Jour. de Med, de Bordeaux," May 8, 1904. Ley, "Revue Francaise de Med. et de Chir.," Oct. 10, 1904. Rooth, "Brit. Med. Jour.," Jan. 24, 1903, p. 197.

[2] See Michelis and Weber, "Brit. Med. Jour.," Sept. 12, 1903, p. 566. Wulff, "Deut. Zeit. f. Chir.," 1901, vol. lviii, p. 478. Bunge, "Arch. f. klin. Chir.," 1901, Bd. 63. Beketoff, "Rousski Vratch," 1903. Morgan, "Jour. Amer. Med. Assoc.," Nov. 29, 1902, p. 1359.

[3] "Amer. Jour. of Med. Sci.," Nov., 1901. See also von Ranke, "Münch. med. Woch.," 1903, No. 1, p. 13.

infectious diseases as typhoid. Attempts to establish a specific microbe for the disease have been unproductive. Clearly the affection is polymicrobic in a large percentage of cases, and in those instances in which but a single microbe has been found the same bacterium is not always present. In Blumer and MacFarlane's cases and in the instances studied by Perthes, von Ranke, and a few others a leptothrix was apparently the cause. In other cases the diphtheria bacillus, staphylococci, streptococci, and various rod-shaped and spiral organisms have been found. In a number of these cases the diphtheria bacillus has been the only organism isolated. The bacillus described by Lingard is present in a small percentage of cases. Noma is fatal in from fifty to seventy per cent. of those affected.

Raynaud's disease,[1] or **digitu mortui,** is a form of gangrene due to arteriovascular spasm. Raynaud, who first described the condition, called it gangrene in the young, thereby distinguishing it from the senile and diabetic gangrenes occurring later in life; it is not restricted to youth. The necrosis is frequently multiple and symmetric, affecting particularly the fingers, ears, and nose; it sometimes occurs in the skin of the trunk and extremities. Osler and others have reported cases tending to show that a similar vascular spasm may occur in the viscera, although in this location it probably never goes on to gangrene. In practically all cases studied, changes have been found in the nerves or vessels, or both. The condition may be associated with acroparesthesia, erythromelalgia, sclerodactylia, and other angioneurotic disturbances.

Morbid Anatomy of Gangrene.—The tissues involved become soft pulp-like, with liquefaction of the fat and cellular elements; as this proceeds blebs form upon the surface and discoloration occurs—reddish-purple, then black, with varying shades of green. Putrefactive bacteria gain ingress and give rise to the chemic phenomena of putrefaction. Gases may be produced, and these, infiltrating the gangrenous tissue, give rise to *gangrenous emphysema* or *gaseous gangrene.*[2] Some cases of gangrene manifest gas production from the beginning, and in others the phenomenon appears late; in many instances gas production does not occur, and the interstitial evolution of gas is practically never present in the so-called dry gangrene. The blood-cells fragment and discolor the fluids, which may be extruded through the skin. The gases of putrefaction give rise to the horribly fetid odor at times present. Where the gangrenous mass joins the living tissue, a *line of demarcation* occurs; this line represents the point at which the tissue is viable, and where tissue death and the processes of infection are arrested, although some of the chemic agents elaborated below this point

[1] The literature of the subject may be traced from the following articles: Savill, "Lancet," June 1, 1901. Osler, "Bull. of Johns Hopkins Hospital," Feb., 1900. Dekeyser, "Jour. Méd. Bruxelles," Nov. 13, 1902, p. 725. Lyle and Greiwe, "Phila. Med. Jour.," Aug. 10, 1901. King, "Amer. Med.," May 17, 1902. Shaw, "Brit. Med. Jour.," March 21, 1903, p. 662. Monro, "Raynaud's Disease," 1899.

[2] Legros, "Recherches Bact. s. l. Gangrènes Gazeues Aigues," Paris, 1902. Dansauer, "Münch. med. Woch.," Sept. 8, 1903. Rist, "Anaerobies Pathogenes et Suppurations Gangreneuses," "Bulletin de l'Inst. Pasteur," Jan. 15, 1905, p. I. Sappington, "N. Y. Med. Jour.," April 2, 1904, p. 641. Kamen, "Centralbl. f. Bakt.," Feb. 18, 1904, Bd. xxxv, No. 5, p. 554. Dudgeon and Sargent, "Path. Soc. of London," Jan. 19, 1904.

may be absorbed. At this line of demarcation embryonic tissue, followed by granulation tissue, develops; these, progressing from the surface, separate the dead from the living tissues; in the soft parts this separation advances with considerable rapidity, while in bone the progress is much slower. In the dead tissue putrefaction proceeds exactly as it would if the tissue were separate from the body; advanced autolytic and liquefactive changes occur in the cells, which eventually liquefy. The gases produced are compounds of hydrogen, sulphur, ammonium, etc.

During the destructive metabolism of tissue, induced and carried on by bacteria, in addition to the products already mentioned are certain chemic bodies always the essential result of microbic growth—ptomains. These, for the most part, are highly diffusible, are rapidly absorbed by the living tissues, and, entering the circulation, give rise to the systemic phenomena accompanying gangrene. It is possible to understand how the intensity of the symptoms depends upon the amount of poison generated in the gangrenous focus, the rapidity of its absorption, and the resistance of the patient.

In spreading gangrene the infection promises to be rapidly fatal by its quick spread and the extreme activity of the toxic substances produced and absorbed; hence, the surgeon lays great stress upon the necessity of immediate removal of the structures in which infection is advancing. The urgency of the case is augmented by the fact that no line of demarcation occurs. In circumscribed gangrene the bacteria present may not be able to invade the adjacent normal tissues possessing their usual degree of resistance. In spreading gangrene, however, the evidence would seem to indicate that the tissue resistance must be reduced or that the bacteria possess the power of infiltrating and destroying tissue not previously injured. By some, spreading gangrene is believed to be an infection of the lymph-spaces, along which the bacteria travel, elaborating their poisons, which, in turn, destroy the adjacent tissue.

(*b*) **Dry gangrene** differs from the preceding in that the less juicy nature of the tissues involved resists infection and the dead structures manifest a marked tendency to mummification. It commonly results from atheroma or obliterative changes in the blood-vessels supplying the part. The skin being unbroken, there is little tendency toward infection and consequent putrefaction. It is associated occasionally with diabetes and other adynamic states in elderly people having the vascular lesions already noted. It is spoken of as *senile gangrene* and as *diabetic gangrene* under the conditions just named.

(*c*) **Hospital gangrene** is now a historic disease, modern antisepsis having led to its disappearance. It probably represented an infection, of extreme virulence, the exact nature of which may be surmised only.

CHAPTER X.

CIRCULATORY DISTURBANCES.

Anemia.—The term anemia is used to designate certain changes in the blood by which its functional capacity is lessened; but, as here considered, reference is made to the **local anemia** dependent upon changes influencing the circulatory apparatus, and not, essentially, upon alterations in the blood itself; it is, therefore, an **ischemia.**

Causes.—(1) Faulty distribution of the blood, as in shock, when the blood tends to accumulate in the larger veins, particularly the splanchnic veins. (2) A very much weakened circulation, whether due to shock, disease, or the influence of poisons, may be too feeble to force the blood through the capillary system, particularly in the skin and brain; hence, cerebral anemia and cutaneous anemia may arise. (3) Diseases of the blood-vessels, such as atheroma; obliterating inflammation of an artery leads to lessened blood-supply in the distribution of the affected vessel. (4) Pressure. (5) Occlusion of an artery, whether complete or partial, as by ligature, pressure of a tumor, thrombosis, or embolism. (6) Spasm of the blood-vessel, due to contraction of its muscle-fibers, either dependent upon or independent of the innervation. (7) An abnormal perivascular pressure in the area involved may lessen the possible ingress of blood. This increased perivascular pressure may arise in a number of ways. Organizing cicatricial tissue may, by its contraction, so increase the pressure normally exerted upon the capillaries that the blood flow may be greatly diminished or even obliterated in some, if not all, of the capillaries of the area involved.

Morbid Anatomy.—The area is pale and bloodless, and the temperature is likely to be lower than normal, or, when the general body-temperature is above the normal, the anemic area manifests a less marked elevation; there may be some edema, and, as will be seen later, the stagnation of regurgitation may be evident.

Effect.—If the ischemia be temporary, there is but slight interference with function; if the process be slowly developed, a gradual lessening of function occurs, and the area may undergo degenerative, necrotic, or atrophic changes; the same result may follow a slight anemia that persists. If the local anemia be sudden y developed and the blood-supply is insufficient to maintain nutrition, death of the part may ensue; such a condition sometimes follows ligation of the main artery of a limb. Local anemia lessens the functional activity of the tissues involved and diminishes their reparative power and resistance to infection. If the flow be greatly reduced or abolished, even for a short time, degenerative changes take place in the capillary walls which increase their permeability and favor the formation of exudates, and sometimes capillary hemorrhages, upon the re-entrance of blood or the re-establishment of the circulation,

or after the occurrence of satisfactory collateral anastomosis. Vascular spasm, lessening the blood-supply to an area, is usually associated with pain, which is most marked at the point of vessel constriction; at the same time there occurs more or less muscle spasm, rendering voluntary movement of the affected part difficult and often painful. The pain of angina pectoris, due to coronary artery disease, the abdominal pains of arteriosclerosis, and the lancinating pains due to sclerotic vessels in the lower extremities appear to be of ischemic origin. Vascular spasm, when involving the leg, and attended by muscular cramps, has been called **intermittent laming** or **intermittent claudication.**

If the arrest of the blood-supply occur in an artery furnishing a branch that communicates indirectly with the area involved, and the circulation be turned through the branch to supply nourishment in the indirect route indicated, such a process is spoken of as *collateral anastomosis.* With the occlusion of an artery the blood-pressure beyond the obstruction gradually lessens until a point is reached when it is less than the pressure in the veins. Backward distention may now occur, so that an area which at one time showed marked ischemia later becomes distended by venous blood. This constitutes the *stagnation of regurgitation*, and probably ends in infarction. (See Embolism.)

Ischemia is sometimes said to be *collateral* or *compensatory* when it results from the accumulation of blood elsewhere.

Hyperemia ("*Active Hyperemia*" or "*Active Congestion*" *of Some Authors*).—This condition is dependent upon an increased arterial influx, a distention of the capillaries by arterial blood, and hence is called *arterial hyperemia*, in contradistinction to a condition, to be considered later, in which the blood present is essentially venous.

Causes.—(1) Physiologic, as the hyperemia of the mucous membranes during digestion or of the uterine mucosa during menstruation. (2) In inflammation, hyperemia constitutes the first stage, and usually persists during the activity of the processes. (3) Increased arterial pressure or tension; ordinarily, it is probable that the greater quantity of the blood is in the venous system, but when there is increased cardiac activity, the arterial and arteriocapillary systems become surcharged; examples of this are seen in the flushed face of active exercise and in the apoplexy that follows violent exertion. (4) *Neuroparalytic*, when the stimulus to the vasoconstrictors is withdrawn. (5) *Neurotonic*, when there is hyperactivity of the vasodilators. (6) Local anemia is, at times, quickly followed by a more or less marked arterial hyperemia. Thus, prolonged pressure not uncommonly produces active hyperemia in the affected area. A similar hyperemia is seen to follow the removal of Esmarch's bandage, applied for the purpose of preventing hemorrhage during the progress of operations. The local anemia produced by cold is frequently followed by an arterial hyperemia. (7) A sudden stroke applied to the skin is quickly succeeded by a local hyperemia, probably depending upon a temporary paralysis of the vasoconstrictors. (8) Certain chemic bodies also induce hyperemia: *e. g.*, mustard, chloroform, cantharides, etc. These probably act by inducing inflammation,—in other words, as irritants,—and the result should therefore be considered with inflammatory hyperemia. Hyperemia is said to be *compensatory* and *collateral* when the blood is forced into one area by reason of its inability to enter another, or as the result of

anemia elsewhere; such a condition is observed in the increased amount of blood sent to one lung when the other is solid or compressed.

Morbid Anatomy.—During life, redness, increased cellular activity and usually a slightly elevated temperature are manifest; swelling discomfort, and, perhaps, pain may accompany the condition; if the process is physiologic, the functional activity is usually increased; in pathologic hyperemia inflammation is likely to occur. Persistent physiologic hyperemia may lead to hypertrophy; similar pathologic hyperemia may cause some of the degenerative processes already described. Postmortem, as the result of emptying of the arterioles and capillaries, the evidence of hyperemia may be wanting. Microscopically, however, there will usually be found capillary rhexis, and, if the process has persisted, degenerative or inflammatory changes may have ensued.

Plethora, also known as **polyemia** and **repletio,** implies an abnormal fullness of the entire vascular apparatus. Several forms have been described, dependent upon the material that is increased in the blood, whether it be an excess in the water in the albuminous compounds or in the corpuscular elements.

Thoma speaks of a **plethora vera,** in which the blood present is normal but the total volume is increased; **hydremic plethora,** as dependent upon an additional quantity of water; again, when the plethora seems to involve the entire vascular system, it is said to be a **general plethora**; a localized form is described that is analogous to congestion, but is sometimes called **vascular plethora.** An overdistention of the lymph-spaces is spoken of as **lymphatic plethora,** a condition closely allied to edema. (See also chapter on The Blood, Part III.)

Hemorrhage.—The escape of all the constituents of the blood constitutes what is ordinarily spoken of as a hemorrhage. Hemorrhages are said to be *arterial*, *venous*, *capillary*, or *mixed*, depending upon the vessel or vessels from which the bleeding occurs. The escape of blood as a result of solution in the continuity of the blood-vessels is called *hemorrhage per rhexin.* The hemorrhages that arise as a result of trauma are properly to be classified with this group. The injury to the vessel may not be sufficient to permit the escape of blood at once, but later degenerative, necrotic, or inflammatory change, attacking the vessel wall, may cause it to rupture. Increased arterial tension is also said to be a cause of hemorrhage. It is probable, however, that the normal blood-vessel, whether it be artery, capillary, or vein, not previously injured or diseased, never ruptures as the result of a simple rise in the blood-pressure. Developing blood-vessels may be exceptions to this rule. When a hemorrhage occurs from a blood-vessel (capillary or vein) without manifest solution in the continuity of its wall, the condition is spoken of as *hemorrhage per diapedesin.* Such hemorrhage occurs as a result of venous obstruction. The increased permeability of the blood-vessels is largely induced through interference with their nutrition, as after persistent local anemia, or as a result of injury, mechanical or thermic, as well as chemic; including under the last-named the destructive influences manifested upon the vascular endothelium by the poisons of many bacteria.

As illustrating the influences of bacteria and bacterial poisons in the production of capillary hemorrhage, the cutaneous, mucous, and

submucous hemorrhages of septicemia, cholera, yellow fever, and allied diseases may be cited. It seems probable that rheumatism is a bacterial affection, and, if so, the capillary hemorrhages present in the disease called **purpura rheumatica** may be of infectious origin. With this group should be considered the so-called **hemorrhagic septicemias.** These are seen particularly in animals, but there can be no doubt that essentially the same condition occurs in man. It is well known that a number of bacteria produce hemolytic poisons, and that blood in which hemolysis is in progress escapes the endothelium of the vessels more readily than in health. Grenet[1] suggests that purpuric affections are produced by the action of toxic substances on the liver. The toxic nature of such hemorrhages is further shown by their most frequent occurrence in connection with infectious diseases. Blair[2] has collected a number of cases of typhoid with multiple subcutaneous hemorrhages. Tripp[3] has observed purpuric hemorrhages in ptomain poisoning. The frequent occurrence of mucous, submucous, serous and subserous, and cutaneous hemorrhages, in leukemia, particularly toward the end of the disease, shows the influence of blood alterations in producing the condition. Wollstein[4] believes that the hemorrhagic affection occurring in the new-born, and called **morbus maculosus neonatorum, epidemic hemoglobinuria,** acute fatty degeneration, syphilis hæmorrhagica neonatorum, and by other names, is an infection not attributable to any specific organism, but may be produced by the Staphylococcus pyogenes albus or aureus, the pyogenic streptococci, pneumococcus, Bacillus pyocyaneus, Bacillus hæmorrhagicus, the Bacillus coli communis the Bacillus enteritidis (Gärtner), and possibly other organisms. The condition may occur in syphilitic infants independently of any other infection. The extensive ecchymoses that occur in phosphorus-poisoning are probably brought about by alterations in the blood and by degenerative changes in the capillary walls. A similar explanation is probably operative with regard to the capillary hemorrhages induced by the poison of venomous reptiles. The presence of bile in the blood is often associated with an increased tendency to hemorrhage; wounds in jaundiced patients often bleed profusely and stubbornly resist the usual methods of hemostasis. Robson believes that the tendency to hemorrhage in jaundice is intensified by the presence of associated pancreatic disease.

In addition to the morbid conditions just considered,—in which it would appear that the occurrence of hemorrhage was dependent upon an acquired alteration in the blood or blood-vessel, or in both, and hence called an acquired hemorrhagic diathesis,—we occasionally find individuals possessing an extraordinary tendency toward the occurrence of severe hemorrhage resulting from the most trivial cause, which tendency seems to have been transmitted from ancestors who manifested the same peculiarity. Such a condition is called *inherited hemorrhagic diathesis*, or **hemophilia.**[5] Hemophilia, or bleeding diathesis, is trans-

[1] Thesè de Paris, 1905.

[2] "Lancet," Jan. 14, 1905, p. 84.

[3] "Northwestern Medicine," June, 1903.

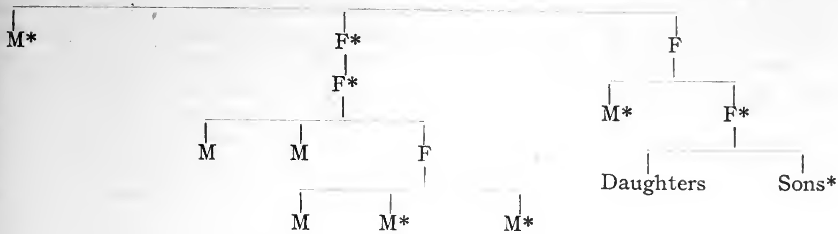
[4] "Arch. of Pædiatrics," Sept., 1904.

[5] Velliet, "Revue de la Méd. Swiss. Romain," Dec. 20, 1902. Carless, "Practitioner," 1903, vol. lxx, p. 85. Grant, "Lancet," Nov. 5, 1904, p. 1279. Greir "Medizinskoe Oborenie," lxi, No. 1. Lossen, "Deut. Zeit. f. Chir.," 1905, vol. lxxvi, p. 1.

mitted commonly from the mother; as a rule, the male children manifest the disease but do not transmit it. The females, on the other hand, usually show no evidence of the affection, but transmit it to their children. No satisfactory explanation has been offered for this congenital hemorrhagic diathesis, although cases undoubtedly occur in which the hemorrhages are arrested by the application of agents favoring the coagulation of the blood. Wright[1] has shown that in some "bleeders" the calcium content of the blood is below normal.

GENEALOGIC TREE OF A HEMOPHILIC FAMILY.[2]

(The persons affected are indicated by an *.)



In addition to the dangers from traumatic hemorrhage, hemophiliacs occasionally manifest a tendency toward other forms of bleeding for which no adequate explanation at present can be given. This peculiarity is sometimes shown by the occurrence of hemorrhage, which may be fatal, from a kidney apparently normal even when submitted to careful microscopic examination (causeless hematuria). Less commonly the hemorrhage without discernible anatomic lesions is from the stomach or intestines. **Hemarthrosis** in hemophiliacs has been especially studied by König, Lucas, Carless, Broca and others. Poillet has analyzed 252 cases; the affected joints are first distended with blood, followed by ecchymosis in the para-articular and subcutaneous tissues. The blood is promptly absorbed, but the bleeding recurs, and eventually the synovial membranes thicken, the fringes hypertrophy, and the articular cartilages become lipped at their free margin and at points pitted. The affection occurs chiefly between the fourth and sixth years of life, nearly all the patients are males, and nearly all the cases that have been operated upon died. The knee is affected in about fifty per cent., and the elbow in about twenty-five per cent. of the cases.

When inflammatory, suppurative, infectious, or ulcerative processes approach the blood-vessel from without and destroy its walls, the consequent hemorrhage is spoken of as *hemorrhage by diabrodosis*, or *hæmorrhage per diabrosin*. Such hemorrhages occur from blood-vessels in the cavities resulting from pulmonary tuberculosis and occasionally are due to suppurative processes around the large vascular trunks of the neck.

The influence of the nervous system in the production of hemorrhage is but little understood. It may act indirectly through the vasomotor system, raising the arterial tension and increasing the pressure in diseased blood-vessels that are already taxed to withstand the

[1] "Lancet," July 5, 1902, p. 15.
[2] Quoted by Lazarus-Barlow from "Schmidt's Jahrbücher," etc., 1863, vol. cxvii, p. 330.

normal stress, and hence, under the increased pressure, give way. Such action of the nervous system fails to explain hemorrhage from the stomach and intestines in diseases of the crura cerebri, and the occasional instances of vicarious menstruation manifested by hemorrhages from the nose, mouth lungs, etc. The hemorrhages of hysteria would seem properly to be classed with this group.

Small areas of hemorrhage with sharply defined margins, at first red then purplish, and eventually purplish-black, are known as *petechiæ*. *Purpuric hemorrhages* manifest themselves by numerous petechiæ principally in the submucous or subcutaneous structures; they are also occasionally observed under serous membranes. An *ecchymosis* is a submucous, interstitial, or subcutaneous hemorrhage, commonly due to injury, but also arising from other causes. Extensive infiltration of the connective tissues by blood is spoken of as *hemorrhagic infiltration*, or *bloody suffusion*, or *suggillation*. When blood collects so as to form a distinct tumor, the mass is called a *hematoma*.

Hemorrhages from various cavities and surfaces have received special names, depending upon their location or on the phenomena to which they give rise: hemorrhage from the nose is called *epistaxis;* hemorrhage from the lungs, *bronchopulmonary hemorrhage*, or *hemoptysis;* excessive menstrual flow is *menorrhagia*, and uterine hemorrhage occurring independently of menstruation, *metrorrhagia;* bleeding from the bowels, *enterorrhagia* or intestinal hemorrhage; hemorrhage from the urinary organs (the blood being voided with the urine), *hematuria;* hemorrhage into joints, *hemarthron* or *hemarthros;* hemorrhage into the brain, *cerebral hemorrhage*, *cerebral apoplexy*, or *hematencephalon;* blood in the pleural cavity, *hemothorax;* a collection of blood in the pelvic peritoneum or in the tunica vaginalis testis is spoken of as a *hematocele;* hemorrhage into the central canal of the spinal cord, *hematomyelia;* hemorrhage into the pericardium, *hemopericardium;* hemorrhage into the peritoneum, *hemoperitoneum;* and so on.

The *effects of hemorrhage* may be local or constitutional. The local changes to be considered are only those that arise in connection with accumulations of blood that remain in contact with the living tissues. Blood acted upon by the digestive juices is more or less modified by the chemic changes which they induce. In the stomach it forms a brown or brownish-black, grumous substance, resembling coffee-ground; hence the term "coffee-ground vomit," used to designate the vomiting of more or less altered blood. Within the intestinal canal the alteration is more marked when hemorrhages have occurred sufficiently high to permit prolonged contact with the intestinal juices. The blood of rectal hemorrhage may escape with but little alteration. When hemorrhages arise in the upper intestine the blood is usually converted into a tarry substance. Blood thrown out into the serous cavities or interstitial tissues, unless excessive, is usually absorbed.

The fate of hemorrhages into the connective tissues is largely dependent upon the amount of blood extravasated and upon the damage to which the tissue has been subjected. When the hemorrhages are small the blood rapidly undergoes hemolysis, the red corpuscles yield their hemoglobin and fragment, and, eventually dissolving, the resulting products are carried away by the lymphatics. The display of color that occurs in bruised areas or areas of local hemorrhage is dependent upon

alterations in the hemoglobin. Distinct collections of blood (*hematomata*), if still communicating with an artery, may remain as false aneurysms. (See Aneurysms.) The small amount of infiltration at the periphery of a blood collection is replaced by cicatricial tissue, which, with the condensed structures, forms a false wall; this structure may limit the hemic tumor or may gradually yield and eventually rupture. Similar collections, not communicating with an artery, usually, in time undergo complete absorption; sometimes, however, such a mass is walled off by a newly formed connective-tissue membrane, which may become calcareous; in time, this may contract and eventually leave nothing but an area of induration. Small residual collections of unabsorbed blood may undergo calcareous change.

The *systemic phenomena induced by hemorrhage* are dependent upon the amount of blood lost and upon the rapidity with which it escapes. A considerable quantity of blood may be lost by a slowly oozing hemorrhage without giving rise to any conspicuous symptom. A much smaller quantity, however, suddenly ejected by an artery, may induce a rapidly fatal issue. In severe hemorrhage the blood-pressure begins to fall coincident with the blood loss. This fall in vascular tension lessens the amount of blood that will escape (in the same length of time under higher blood-pressure the loss would be greater), and favors the occurrence of coagulation, at the same time permitting contraction of the blood-vessel. The sudden drop in blood-pressure, and the associated faulty distribution of the blood, give rise to cerebral anemia, which, if the fall be marked or long continued, may terminate fatally. Under lower blood-pressure a clot not uncommonly forms in the wounded vessel, and with the complete arrest of hemorrhage the volume of blood is made up as soon as possible by removal from the lymph-spaces of the available fluid in the body, gradually restoring the circulatory volume and paving the way to complete regeneration of the blood. (See Blood.)

Lymphorrhea or **lymphorrhagia** is the abnormal escape of lymph usually due to some solution in the continuity of the larger lymph-vessels. The same term is made to embrace the escape of chyle from the lacteal system or thoracic duct, a condition usually due to the injury of these structures or to the presence of thrombosis or an animal parasite occluding the lumen.[1] Wounds or rupture of the thoracic duct may permit the chyle to enter the peritoneum (chylous ascites) or pleura (chylothorax).

The condition which I shall describe as **congestion** is also known as *venous hyperemia* or *venous congestion*, *passive hyperemia* or *passive congestion*. It results from faulty exit of the blood, and consequent retarded flow, giving rise to accumulation in the veins and capillaries of the area involved. In contrast to hyperemia, in which there is an increased amount of arterial blood, in congestion there is an increased amount of venous blood.

Causes.—Any condition that prevents free venous exit, and that at the same time does not limit arterial ingress; pressure, and constricting bands that compress the easily collapsed veins and not the more rigid arteries; diseases of the veins, such as inflammation and thrombosis, which narrow the lumina and lessen the carrying capacity

[1] See Elephantoid Diseases, p. 210.

of the affected vessels; tumors, and pressure from surrounding or adjacent organs or structures. In a feeble circulation congestion is favored by the influences of gravity, as in the congested extremities of individuals suffering from valvular heart-disease. Venous and capillary distention, dependent upon feebleness of the circulation, is illustrated in the **hypostatic congestion** of the lungs that accompanies typhoid fever and other adynamic states. Arrest of arterial flow may lead indirectly to congestion depending upon the regurgitation of blood from veins in which a more or less constant pressure is maintained; such vascular distention, at first manifested in the larger veins, but sooner or later reaching the venules and capillaries, is termed the *congestion of regurgitation*.

Morbid Anatomy.—This is largely dependent upon the duration of the process and its magnitude. During life the area involved is edematous, swollen, and bluish, with a temperature usually lower than normal. The cause of the associated swelling will be further considered when dealing with edema. The gradual reduction in circulatory activity gives rise to overdistention of the capillaries of the area involved, degenerative changes in their walls, and, if prolonged or intense, diapedesis, and corpuscular plugging. The distention of the capillaries by plugs in which the cellular elements may no longer be recognized (stasis) is frequently seen. As a result of hemolysis affecting the quiescent red blood-cells, both within and without the blood-vessels, a certain amount of pigmentation may be present, particularly where the process has been long continued. Prior to complete stagnation and dissolution of the cellular elements restoration of the circulation is possible. The process is likely to terminate in degenerative, atrophic, or necrotic changes in the affected tissues; this is due to the fact that nutrition in any given area is as dependent upon the removal of the products of cell life as it is upon the supply of pabulum. If the area involved be large, and the process be sufficiently marked, coagulation necrosis, followed by gangrene, may occur. Such extensive necrotic processes are, of necessity, preceded by stasis. Congestion is likely to persist postmortem and to be evident, thereby differing from hyperemia. The form of congestion that develops after the cessation of circulation, known as *suggillation*, must be differentiated from congestion that arose during life. Postmortem suggillation is not usually accompanied by edema, and the affected tissues do not show the nutritive changes that accompany antemortem venous stasis. (See pages 5 and 6.)

Stasis.—When, as the result of slowing the circulation, the obstruction of gravity, inflammation, or of injury, the blood stops circulating in the capillaries of an area, the condition is called stasis. It is a very common sequence of congestion, occasionally occurs in hyperemia, and is a more or less constant phenomenon in inflammation. The extent of stasis in inflammatory processes is dependent upon the activity of the inflammation and upon the recuperative powers of the circulation. The virulence of the infection is no doubt also a determining factor. In addition to the causes just mentioned, stasis occasionally arises as a result of tension occluding the blood-vessels to or from an area, and may also be caused by inspissation; as, for example, from prolonged exposure of serous surfaces, notably the peritoneum.

The corpuscular changes terminate in dissolution, fragmentation of the cells, and not infrequently necrosis of the capillary walls; the necrotic process may also involve the perivascular structures.

Edema[1] implies abnormal or excessive transudation of the fluid portion of the blood into, or its unusual retention in, the lymph-spaces. As the large serous cavities are generally conceded to be lymph-spaces, the accumulation of serum such as is seen in the ascites that may accompany cirrhosis of the liver belongs truly to the edematous condition.

Causes.—The pathology of edema is intimately associated with the normal process of lymph formation. When physiologists satisfactorily determine the origin of lymph, we shall be better able to appreciate the overdistention of the lymph-spaces seen in edema. It is probable that the cause of edema is never a single factor, usually depending upon a combination of conditions, among which may be considered alterations in the blood, in the blood-pressure, and in the capillary wall and interferences with the normal flow of lymph. To these may possibly be added decreased perivascular pressure, and possibly chemic and structural changes in the tissues; that the nervous system may exert a certain causative influence can not be overlooked, but the nature of the factor or the manner of its action can not be so accurately determined. Some are inclined to believe that abnormalities of the blood will not produce edema until sufficient time has elapsed for the blood alterations to give rise, either directly or indirectly, to changes in the vessel walls. The changes in the vessel walls consist, for the most part, of alterations in the endothelium of the capillaries. The endothelium may become granular, cloudy, or even partially exfoliated. With such alterations the endothelium possibly becomes more permeable, or separation of the endothelial plates along their line of juncture may be thought of. It is probable that in all forms of edema, arising from increased blood-pressure, some change in the endothelium is an essential part of the process. When there is an obstruction to the onward flow of the blood, such as may occur from ligation or occlusion of the principal veins, or when there is retardation in the progress of the blood, increasing the pressure in the capillaries and leading to such degenerative changes in the endothelium as to permit extravasation of serum, edema

[1] The literature of edema is very extensive. The most important can be traced from the following articles: Chantemesse and Podwyssotsky, "Les Processus Généraux," 1905, vol. ii, p. 331. Meltzer, Harrington Lectures, University of Buffalo, 1904, reprint; also "American Medicine," July 9, 16, 23, and 30, 1904. Burnet, "International Clinics," 1904, vol. iv, 13th series. Harrington, "Boston Med. and Surg. Jour.," March 30, 1905, p. 362. Merklen and Heitz, "Bull. de la Soc. Méd. de Paris," Jan. 21, 1904, p. 26. Bodin, "Pflüger's Arch.," Sept. 30, 1904. Apert and Delille, "Lancet," Jan. 7, 1905, p. 43. Baum, "Berl. klin. Woch.," Jan. 2, 1905. Valobra, "Soc. de Neurol. de Paris," March 2, 1905. Sainton and Voisin, "Nouv. Iconogr. de la Salpêtrière," May–June, 1904. Achard, Lemierre and others, "Soc. des Méd. des Hôp.," July 25, 1903. Courmont, "Lyon Méd.," July 12, 1903, p. 33. Dopter and Tanton, "Bull. et Mem. de la Soc. Méd. des Hôpitaux de Paris," July 18, 1901, No. 25. Albu, "Virch. Arch.," 1901, Bd. 166, S. 87. Bolton, "Jour. of Path. and Bact.," Aug., 1903, p. 67. Loeper, "La Presse Méd.," Sept. 25, 1903, p. 630. Widal and Javal, "La Presse Méd.," Oct. 7, 1903, p. 701. Castaigne and Rathery, "Arch. de Med. Exper.," Sept., 1903, p. 669. Kövesi and Róth-Schulz, "Wien. klin. Woch.," Oct. 13, 1904. Morris, "Amer. Jour. of Med. Sci.," Nov., 1904, p. 812. Osler, "Amer. Jour. of Med. Sci.," Jan., 1904, p. 1. Fairbanks, "Amer. Jour. of Med. Sci.," Sept., 1903, p. 443; also May, 1904, p. 877. Kurt, "Zieg. Beitr.," 1904, Bd. 36, p. 435.

results. Similarly venous congestion, due to inability of the heart properly to advance the venous blood, may induce a similar lesion, called cardiac edema. That edema produced by obstruction to the onward flow of the blood is directly due to the increased intracapillary pressure can not be said definitely to be demonstrated. It is probable that it arises, in part at least, as a result of associated degenerative changes in the endothelium, increasing the permeability of the vascular wall and permitting the occurrence of serous transudation.

The fact that the blood-vessels in an edematous area may show no recognizable structural lesion has led to the belief that edema may, under certain circumstances, be dependent upon an increased secretory action of these cells, presuming, of course, that the normal lymph is produced by a process of secretion and not simply by transudation. The presence of certain materials in the circulation undoubtedly favors the occurrence of edema. For the most part these are toxic substances, of which bacterial poisons may be taken as examples. It is not improbable that they increase the diffusibility of the serum and at the same time injure the endothelial cells. The edemas that occur in the last stages of tuberculosis, and in various cachexiæ associated with lowered nutrition, are probably dependent upon the faulty nourishment of the vascular endothelium as well as upon alterations in the blood, and in not a few of these the presence of toxic materials in the circulating fluids can not be positively excluded as adjuvant factors. The influence of tissue tension in the occurrence of edema must not be overlooked. With vascular changes practically the same, edema must, of necessity, occur with more rapidity in lax tissues, such as the eyelid and scrotum, than in tissues of greater density, such as periosteum and bone. Normally, the nutrition of the tissues is maintained, in part at least, by serum passing out from the vessels into the perivascular structures (primitive lymph-vessels); the cells abstract from this fluid the elements necessary for their nutrition, and yield to it excrementitious products, after which it is removed from the tissues by the lymph-stream. It will be seen that any obstruction to the onward flow of the lymph, such as may result from pressure upon the lymph-duct, may give rise to an accumulative edema in the area drained without the necessity of presupposing any degenerative change in the blood-vessels of the part.

As a result of the studies of Widal, Achard, Loeper, and other French observers, great stress is at present being laid on the relation between the sodium chlorid content of the tissues and the occurrence of edema. If for any reason an excess of this salt be present in the connective or other tissues, the attempt to maintain isotonicity results in an excess of fluid accumulating in the structures containing the abnormal amount of sodium chlorid. It is not certain that any other salt exerts exactly the same action. This theory of edema formation has been turned to therapeutic advantage; dropsical patients are given salt-free diet and elimination of the sodium chlorid facilitated in every way possible. The results seem to add support to the theory upon which the treatment is based. Admitting the correctness of the French observers, the necessity for explaining the excess of sodium chlorid is no less urgent than the original proposition. The fact that salt excretion is

less active during certain inflammations (croupous pneumonia) and intoxications, indicates that the substance constitutes an important part of the protective influences of the body, and is especially necessary in resisting bacteria, bacterial toxins, and some other poisons. Tissues subjected to the action of toxic bodies may extract salt from the circulating fluids, and this in turn be followed by an accumulation of serum. It has been demonstrated that in renal, and sometimes, although not invariably, in cardiac dropsies, the sodium chlorid content of the affected tissues is above the normal.

However the edema fluid enters the lymph-spaces or lymph-vessels, and whatever may be the cause of its accumulation, there is no reasonable doubt as to its origin; it is derived from the liquor sanguinis, from which, however, it differs in the lessened proteid content, the usual absence of all the factors necessary to form fibrin, its lower specific gravity, and minor differences in the proportion of salts.

The studies of Merklen and Heitz, and also Kostkevitch, have shown conclusively that most edema fluids contain toxic substances, and that, when rapidly absorbed, may give rise to nervous, cardiac, and renal disturbances. The character of these poisons no doubt differs and is largely determined by the cause of the edema. When removed, the absorption of edema fluids is accomplished by the blood-vessels, principally the veins, and by the lymphatics.

A form of edema known as **edema ex vacuo** is said to occur when brain-tissue or tissue from the spinal cord disappears by any process, and the resulting cavity, or loss of structure, or shrinking of the organ, must be filled in.

Edema is often named for the cause that gives rise to the lesion in the blood-vessel or blood primarily. Such edema may be known as *toxic*, *infectious*, *cachectic*, *traumatic*, *ischemic*, *inflammatory*, *thermal*, or, in some cases (as when the dilatation of the blood-vessels is dependent upon errors or lesions in innervation), the condition may be spoken of as *trophic edema* or *neuropathic edema*.

Morbid Anatomy.—Edematous tissue is usually pale, pits on pressure, and as a result of the deficient circulation of the blood, is lower in temperature than the normal. On incision serum escapes, and the watery condition of the tissue can be readily seen. By reason of the deficient circulation, the resistance of such tissue is lowered, and this renders it extremely susceptible to infectious and necrotic processes. Not uncommonly the edematous tissue shows well-marked and advanced degenerative changes. (See Hydropic Degeneration, p. 245.) Edema fluids, spoken of as *transudates*, differ in some respects from inflammatory accumulations, called *exudates*. The former possess a low specific gravity, are poor in cells, and contain a relatively small proportion of albumin. A specific gravity of 1016 to 1020 is not uncommon in inflammatory exudates, while dropsical collections rarely attain a specific gravity of 1015, usually falling below—1009 to 1010. Transudates are commonly clear and poor in cells, of which the mononuclear leukocytes and endothelium are most numerous; exudates are turbid and usually rich in leukocytes.

The histologic studies of Kurt show that in edematous tissues the fibrous and elastic elements are swollen, hyaline, and often fragmented. Lymph-spaces are more or less dilated, and usually contain an abnor-

mal number of leukocytes, especially of the mononuclear type. The affected epithelial cells imbibe an excess of fluid and frequently show the so-called hydropic spots or vacuolated areas; fragmentation and deficient tingibility are practically always present in the chromatin of cells in edematous areas. The cells of the central nervous system in edema affecting the brain, cord, or meninges are similarly altered.

Different names have been given to the accumulations of dropsical fluids, based upon the location, cause, or admixture with other fluids. When the edema is more or less general, the term *hydrops universalis* is applied; edema of the connective tissues, particularly of subcutaneous connective tissues, is called *anasarca;* dropsy of the peritoneum is spoken of as *hydroperitoneum* or *ascites;* dropsy of the pleura as *hydrothorax*, which condition may be unilateral or bilateral; dropsy of the pericardium, as *hydropericardium;* fluid accumulation in joints, as *dropsy of the joints* or *hydrops articuli.* Fluid accumulation in the cerebral ventricles is called *internal hydrocephalus*, and when the excess is in the meninges or brain substance, cerebral edema; the latter is also known as external hydrocephalus. The origin of edematous collections is sometimes indicated by the name: as, for example, renal dropsy, cardiac dropsy, congestive dropsy, angiosclerotic edema (edema associated with sclerotic changes in the blood-vessels). Reference has already been made to the toxic, infectious, and other forms of edema.

THROMBOSIS.

A **thrombus**[1] is a more or less uniformly solid or semisolid body, formed during life in the heart or blood-vessels and resulting from causes that lead to the agmination, agglutination or coagulation of one or more elements present in the blood. The older definition—an antemortem intravascular clot—did not take into consideration the agmination and agglutination of platelets and leukocytes Many thrombi, however, are nothing more than fibrinous coagula, relatively rich in leukocytes and platelets. The term **thrombosis** is applied to the process terminating in the formation of a thrombus. It is also somewhat loosely used to cover the associated conditions.

In most instances there is little difficulty in differentiating thrombi from postmortem clots. Coagula formed after death have certain points that are highly characteristic; they are usually smooth on the surface, and show no attachment to the vessels in which they lie although they may be entangled: as, for example, in the muscular columns or the tendinous cords in the heart. This absence of attach-

[1] Welch, "Allbutt and Rolleston, System of Med.," vol. vi. Steiner, "Bull. Johns Hopkins Hospital," June, 1902, p. 130. Flexner, "Univ. of Penna. Med. Bull.," Nov., 1902. Pearce-Gould, Lettsonian Lectures, "Lancet," June 7, 1902. Clark, "Univ. of Penna. Med. Bull.," July, 1902. Orlowski, "Russki Vratch," vol. ii, No. 6. Moore, "Lancet," Dec. 19, 1903, p. 1715. Loeb, "Montreal Med. Jour.," July, 1903. Gerster, "Trans. Amer. Surg. Assoc.," 1903. Mignon and Dopter, "La Presse Méd.," Oct. 29, 1904, p. 689. Pearce and Winne, "Amer. Jour. of Med. Sci.," Oct., 1904. Weinberger, "Wien. klin. Woch.," Jan. 21, 1904, p. 64. Aldrich, "N. Y. Med. Jour.," March 5, 1904, p. 442. Osswald, "Deut. Zeit. f. klin. Med.," vol. 53. Goldsborough, "Johns Hopkins Hosp. Bull.," June, 1904, p. 193. Thayer, "Med. News," Oct. 1, 1904, p. 637. Le Tohic, Thesè de Paris, 1904. Chantemesse and Podwyssotsky, "Les Processus Généraux," 1905, vol. ii, p. 134, bibliography.

ment is highly important; even when a thrombus has been dislodged from its place of origin, the point from which the thrombus has been detached can usually be easily recognized as a roughened area upon the blood-vessel or heart wall, cardiac orifice, or valve leaflet. In many instances an area on the thrombus that shows evidence of past attachment can be found. The postmortem clot possesses a moist, glistening surface, is usually red in color; some part of it always shows the redness due to red blood-cells, and an important differentiation, for which we are indebted to Cohnheim, is that in the thrombus there is little difficulty in accomplishing longitudinal splitting. The thrombus usually has a frayed-out end. A postmortem clot does not show the changes that may be seen proceeding in a thrombus. (See p. 275.) Occasionally, where postmortem coagulation of the blood goes on very slowly, sufficient time elapses for the red blood-cells to settle to the most dependent portion, giving rise to a clot the upper layers of which are colorless and jelly-like, while the lower stratum shows a deeper color than usual by reason of its richness in red blood-cells.

Very often, when life is almost extinct (agonal period), the very slow rate at which the blood is flowing may favor the occurrence of thrombi, which, later, become continuous with postmortem clots, coagulation going on around the thrombus after death. While not restricted to the right side of the heart and the pulmonary artery, such clots frequently cocur in that location.

Red thrombi contain blood coloring-matter usually in the entangled red blood-cells; these are the thrombi that form in stagnant or practically quiescent blood. **White thrombi** are thrombi consisting of fibrin with a varying number of leukocytes and blood-platelets, and are formed in flowing blood. Thrombi may be mixed—the so-called **gray thrombi,** in which the gradual slowing of the blood has led to a slight deposit of red blood-cells with the forming and condensing fibrin. As a result of ribbed, "frayed-out," or irregular thrombus-formation, longitudinal cavities are sometimes produced in which the more or less quiescent blood proceeds to clotting, and thereby becomes a part of the completed thrombus. This condition gives rise to thrombi that may be, in a sense, mixed, certain parts being distinctly red, other parts gray, and still other areas red and jelly-like, closely resembling the thrombi formed elsewhere in quiescent blood. When the mass is composed of layers, such as occur in the cavity of an aneurysm, the thrombus is said to be **stratified.** When a thrombus remains where it originated and arises independent of other thrombi, it is called a **primary thrombus.** The term **propagated thrombus** is applied to a thrombus that extends some distance from the point at which it originated; such thrombi are extremely likely to show different ages at different points, and may extend to an indefinite length. A thrombus developing from an embolus, or a thrombus that arises secondary to an existing thrombus, is known as a **secondary thrombus.** When a thrombus leads to occlusion of the blood-vessel or cardiac orifice in which it lies, it is said to be an **obstructing thrombus.** When it permits the blood to flow one way and occludes a current flowing in the opposite direction, it is termed a **valve thrombus.** When the thrombus lines the wall of a cavity,—*e. g.*, an aneurysm or a blood-vessel,—it is known as a **parietal** or a **mural thrombus.** When a thrombus extends around a blood-vessel

it is said to be **annular**; if formed with a distinct canal, it is spoken of as a **channeled** or **canalized thrombus.** The "*ball thrombus*" is not attached, although evidence of recent attachment may be present either on the thrombus or on the vascular or cardiac wall; a point of separation from a fragment, still attached, may often be recognized. Ball thrombi are most frequently found in the dilated left auricle in cases of mitral stenosis. Polypoid or pedunculated thrombi, so-called *cardiac polypi*, are most frequently seen in the left auricle; the point of attachment is usually the margin of the fossa ovalis or its immediate vicinity. The pedicle, and not uncommonly a larger part of the thrombus, may show advanced organization. The structure of such partly organized polypi may resemble fibrous or myxomatous tissue, and hence they have been termed *fibromatous* and *myxomatous polypi* respectively. An endothelial covering is sometimes demonstrable, and calcareous infiltration may be in an early stage or even advanced.

The most important division of thrombi is into **simple** or **bland,** and **infected** or **infective,** the former including the aseptic thrombi, containing no bacteria, the latter terms being applied to thrombi in which bacteria are present, hence *infected thrombi*. A further division of infected thrombi has been proposed. It is suggested that the term septic thrombi be applied to those in which organisms of suppuration are present, and the term putrid thrombi to those that contain bacteria of decomposition. The fact that the bacteria of decomposition may be present alone or associated with the organisms of suppuration deprives such a division of much of its theoretic value.

Thrombi are sometimes called **arterial** or **venous,** and, under the latter, a separate form is named, dependent upon its location in a distinct venous system—**portal thrombi.**

Causes.—The essential exciting cause of a thrombus is that process terminating in coagulation of the blood. Other causes are: (1) Any body within the circulation, not covered by endothelium, leading to attachment of blood-platelets and to the subsequent formation of a clot or thrombus; (2) roughening of the vascular wall, as observed in atheroma; (3) slowing of the circulation, such as occurs in partial occlusion of a blood-vessel, or in complete obstruction, as represented by ligation. It is maintained, and probably justly, that a blood-vessel may be ligated and its lumen occluded without the intervention of a clot. This implies great care in applying a ligature, so that it does not injure the endothelium. When a blood-vessel is ligated in its continuity, two thrombi are usually formed: one on the cardiac side, known as the **proximal thrombus,** and a second in the blood-vessel, beyond the point of ligation, known as the **distal thrombus.** It is probable that complete or partial obstruction gives rise to changes in the endothelium of the vessel wall, and this favors the mural lodgment of leukocytes and third corpuscles, and hence of a thrombus. As will be noted later, the formation of a thrombus is not essential to the obliteration of a blood-vessel in which the circulation has ceased. Indeed, it is held by some authors that thrombosis interferes with the obliterative endarteritis that normally leads to the disappearance of a blood-vessel. (4) Any alteration in the vessel wall that injures the endothelium favors the development of a thrombus. (5) Chemic changes in the blood also facilitate the occurrence of thrombosis; thrombi

partly due to this cause are seen in diphtheria and in adynamic conditions with very much slowed and enfeebled circulation. Such thrombi are called **marasmic thrombi.** (6) Hyperinosis, such as develops in pregnancy, is nature's method of anticipating hemorrhage, the increased amount of fibrin favoring the arrest of bleeding by the development of thrombi. Hyperinosis is not of itself an exciting cause of thrombosis, as many conditions are associated with an increase in the amount of fibrin-forming elements in the blood without any marked tendency toward the occurrence of thrombosis. (7) Chemic changes leading to a thrombus may be produced in the blood by the injection of certain agents: *e. g.*, ether. (8) Where a tumor infiltrates, comes in contact with, or penetrates a blood-vessel, a thrombus frequently forms. (9) A primary thrombus favors the development of secondary thrombi. (10) Mycoses of the blood may give rise to or follow thrombosis. (11) Embolism often leads to thrombus-formation.

The old discussion as to whether thrombosis depended upon changes in the blood, or alterations in the vessel wall, appears to have been satisfactorily settled. Bacteria or bacterial products in the circulating blood acting upon the vessel wall alter the endothelium, favor the deposit of platelets or leukocytes, thereby forming a nucleus upon which thrombus formation progresses. The studies of Eichhorst, Steiner, Thayer, and others have clearly established the influence of infectious diseases on the production of thrombosis. Eichhorst was able to collect 42 instances of thrombus formation in typhus, 40 in typhoid, and 19 in influenza. He believes that the thrombus formation, in certain instances at least, is due to bacterial invasion by way of the vasa vasorum. Steiner found 41 instances of thrombosis complicating pneumonia; Orlowski was able to collate 38 cases in which thrombosis of the abdominal aorta complicated infectious disease. Thayer analyzed 42 cases of venous thrombosis occurring in the course of typhoid fever. Thromboses of the uterine sinuses and of the pelvic and saphenous veins are not infrequently results of septic processes in the uterus, parametrium, or pelvic tissues. Flexner's studies on the *intra vitam* agglutination of red blood-cells throw considerable light on the formation of thrombi in hemolytic processes, and it may be possible that the thrombosis of chlorosis has a similar origin. The so-called marantic thrombi, long held as occurring independently of infection, are probably bacterial in origin. Harris and Longcope found demonstrable bacteria in 34 of 44 studied. The observations of Clark strongly incline toward the belief that trauma may produce thrombosis without the presence of bacteria, or at least in the absence of discernible infection. The extension of inflammatory or septic processes from the perivascular tissue is easily recognized as an important cause of thrombosis. Veins are frequently thrombosed as a result of infection involving the area in which their branches are distributed. In inflammations and infections of the appendix, thrombi may be propagated along the course of the portal vessels, constituting one of the important causes of hepatic abscess due to embolism from the portal vein. In a like manner the cranial sinuses may be infected from septic processes in the contiguous bone, particularly the middle ear and mastoid. Pearce-Gould calls attention to the frequency with which thrombosis manifests a tendency to relapse, and cites a case in which, during twenty-five years, a man

was invalided, at different periods, for six years and two months on account of thrombosis, the origin of which was obscure.

Thrombus formation begins as a thromboarteritis, thrombophlebitis, or thrombosinusitis with alteration of the lining endothelium of the affected vessel, the deposit of platelets, and possibly leukocytes, fol-

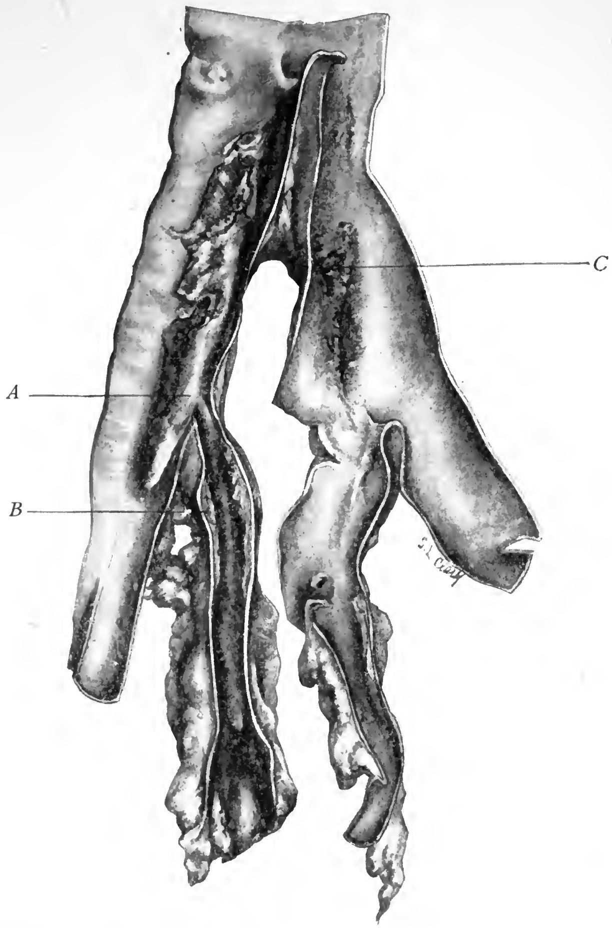


FIG. 146.—TERMINATION OF AORTA, THE COMMON ILIAC, EXTERNAL AND INTERNAL ILIACS, CASE OF THROMBO-ARTERITIS DUE TO PARA-UTERINE INFLAMMATION AND EXTENSION TO THE VESSELS FROM ADJACENT TISSUES.

A. Thrombus in common iliac artery secondary to and an extension from the primary thrombus in the right internal iliac. *B*. Point of initial thrombo-arteritis with partial organization of a peripheral gray thrombus; the central more recent thrombus was red. Note the great thickening of the artery and periarterial tissues. *C*. Left common iliac the seat of acute endarteritis, upon which a thrombus is just beginning to form.

lowed by superimposed fibrin. The area of attachment in the involved blood-channel depends upon the extent of the endothelial erosion. From its point of origin a thrombus may be propagated in either direction, but usually the extension is farthest in the line of the blood-current.

Changes That a Thrombus May Undergo.—The character of the transformations observed in thrombi are dependent upon whether the process is *simple* or *infective*. In **infective thrombi** the only changes that are likely to occur are those constantly associated with infection: namely, *liquefaction*, *softening*, or fragmentation and other alterations that commonly accompany necrosis; rarely, in infected thrombi, dislodgment may occur. With the exception of softening the changes to be considered in *simple thrombi* seldom take place in infected thrombi. The fragments of an infected thrombus become infected emboli, and lead to dissemination of the infective material and to its deposit in other parts of the body; besides this, infected thrombi are constantly throwing into the circulation bacteria, or the products of bacterial life, this condition constituting what is known as *septicemia*, *bacteremia*, or *mycosis* of the blood. When the infected material contains pyogenic organisms, the emboli, lodging, give rise to abscesses; such abscesses are spoken of as *pyemic* or *metastatic*, and the disease is known as *pyemia*. Before the elucidation of the subject of blood-poisoning, afforded by our knowledge of bacteria and infectious processes, it was presumed that metastatic abscesses resulted from the presence of pus in the blood; hence the name *pyemia*. It is now known that the condition is due not of necessity to the presence of formed pus, but to agents capable of inducing suppurative processes—bacteria.

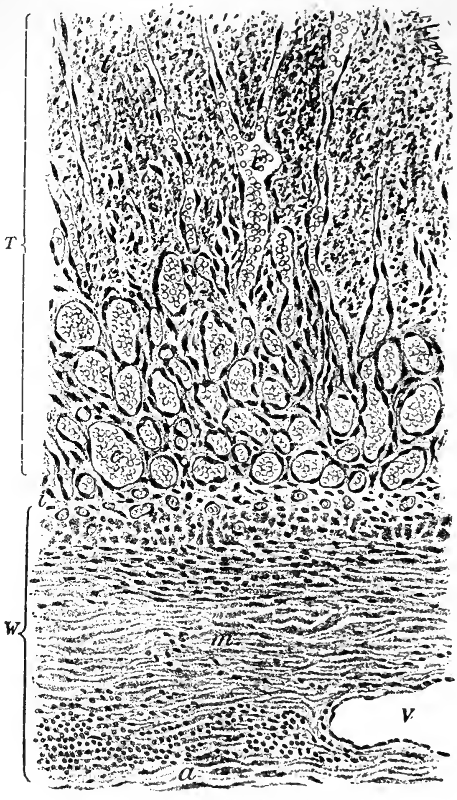


FIG. 147.—SECTION THROUGH A PART OF A VEIN WITH ITS CONTAINED ORGANIZING THROMBUS.—(*Schmaus.*)

W. Wall of vein. *a*. Adventitia. *m*. Media. *i*. Intima. *V* Blood-vessel in the wall of the vein. *T*. Thrombus, now largely composed of granulation tissue. *c*, *c*, *c*. Young blood-vessels; those near the intima are larger and more fully developed than those extending into the thrombus, the latter being younger.

The following changes may occur in thrombi:

1. Dislodgment occurs but rarely. The cases that the writer has observed have been from large tumors of the uterus, where a thrombus had formed in one of the massive sinuses of such a tumor, and, becoming dislodged, had reached the lung and blocked the larger vessels to that organ, leading to almost instant death. Dislodgment of a thrombus is favored by any sudden increase in the rapidity of the

circulation, particularly when the accelerated current is brought directly in contact with the thrombus; manipulation of the diseased part, or even comparatively slight muscular movement in an affected limb, when an extremity is involved, may detach a loosely adherent thrombus. A ball thrombus, in the left auricle, may become jammed into the mitral orifice.

2. *Decolorization* is possible only in the red thrombus, and is due to the gradual absorption of the coloring-matter by the circulating blood, which flows over, around, or through it, and to the removal of precipitated coloring-matter by phagocytic cells.

3. It is difficult, if not quite impossible, to demonstrate the occurrence of *re-solution;* but there can be no doubt that the simple, non-infected thrombus, due to temporary conditions, may be dissolved or may undergo solution upon the removal of the cause.

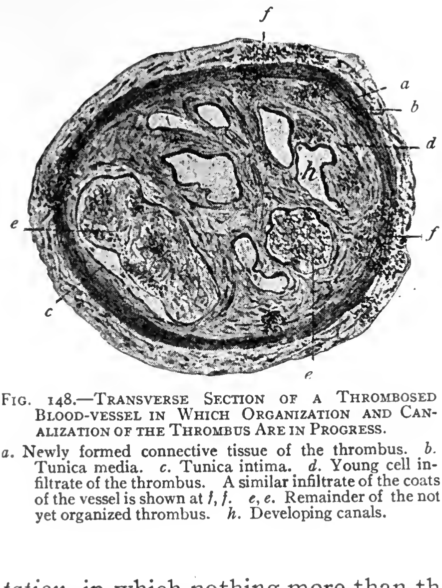


FIG. 148.—TRANSVERSE SECTION OF A THROMBOSED BLOOD-VESSEL IN WHICH ORGANIZATION AND CANALIZATION OF THE THROMBUS ARE IN PROGRESS.

a. Newly formed connective tissue of the thrombus. *b.* Tunica media. *c.* Tunica intima. *d.* Young cell infiltrate of the thrombus. A similar infiltrate of the coats of the vessel is shown at *f, f.* *e, e.* Remainder of the not yet organized thrombus. *h.* Developing canals.

4. *Softening* is not so common in the simple as in the infected thrombus, and is usually due to conditions of development, to the location and size of the thrombus, and to blood changes and infection that militate against the process of organization. When this change occurs without infection, it is termed *simple softening;* when bacteria are present, *septic* or *infective softening.* When softening and disintegration occur, the fragments, reaching the circulation, form *simple* or *infective emboli*, depending on whether the thrombus contained viable organisms or not; more commonly, instead of softening, there is really a condition of *fragmentation*, in which nothing more than the end of a thrombus is broken off.

5. *Organization* is possible only in the absence of infection. It may occur in infected thrombi after the subsidence of infection, although upon this point there must remain much doubt. The conversion of the thrombus into connective tissue is effected largely through the activity of the endothelial cells of the intima. Before the beginning of organization considerable contraction is usually brought about by removal of the fluids present in the thrombus, and possibly by a certain amount of liquefaction and absorption. Where the thrombus becomes continuous with the intima, the endothelium gradually extends over its surface. From this endothelial covering, processes of young connective-tissue cells extend downward into the thrombus, forming capillaries. A similar proliferation of any viable endothelium beneath the thrombus also takes place, and young blood-vessels from the adjacent nutrient branches are pushed forward into the prolifer-

ate. During the extension of this embryonic tissue formation further absorption and shrinkage of the thrombus occur. Gradually the new connective tissue replaces the thrombus and organization of the cicatricial tissue is completed as usual. (See Process of Repair.) The activity of the leukocytes in this process is no longer conceded to be important. With the presence of infection large numbers of leukocytes may be found. They are not, however, regarded as essential elements in the production of the formative tissue through which organization is eventually completed. The influence of the organized body upon the blood-vessel will be, of course dependent upon the extent and location of the thrombus and upon the completeness with which it occludes the vascular lumen. The effect of the subsequent cicatricial contraction is shown by the deformity that it induces, and is particularly marked in the organized thrombi that constitute the vegetations on the valve leaflets in endocarditis. (See Results of Endocarditis.)

6. When a thrombus forms in a slowed circulation,—*e. g.*, of a dilated vein,—and is attached to the vessel or lodged in the sinus of a valve, infiltration by lime salts—calcification—not uncommonly occurs, producing the so-called *phleboliths*, or "*vein stones*"; arterioliths and stone-like concretions attached to the cardiac walls or orifices are produced in a similar manner; infiltration of lime salts is also likely to occur in a thrombus that is organizing or that has organized.

Modifications of some of the foregoing conditions are occasionally considered as separate processes; thus, a large thrombus may exhibit a *central softening*, and postmortem or during an operation—*e. g.*, on aneurysm—a thrombus may be found in which liquefaction necrosis has occurred, converting the center of the mass into a reddish or yellowish fluid; this was at one time spoken of as cystic degeneration of a thrombus; probably it is an autolytic process. An attached thrombus may remain more or less quiescent for a considerable length of time, or the changes that it undergoes may be so poorly marked as to be scarcely recognizable.

Results of Thrombosis.—These are largely dependent upon the character, location, and cause of the thrombus and upon the changes that the thrombus itself has undergone; the results due to such changes will suggest themselves: *e. g.*, an organizing or obstructing thrombus may more or less fully occlude the blood-vessel; the evidence of such occlusion depends upon whether the blood-vessel is the main trunk to a limb or one of the less important branches; again, if the thrombus form slowly, the collateral circulation may sustain the nutrition of the part. The alterations produced in the blood-vessel are dependent upon the changes that the thrombus undergoes; these also suggest themselves or have been indicated.

Thrombosis may affect lacteal, chylous, and lymph-vessels, producing alterations that are not unlike the changes seen in blood-channels. The lessened force of the current renders lymphogenous embolism infrequent and obliteration of the vessel common. The process, although rare, is sometimes seen in the thoracic duct, and may be due to extension of thrombosis from the subclavian or jugular vein. Tuberculosis or other infective disease in the tissues around the thoracic duct may extend through the wall and be propagated from the interior.

EMBOLISM.[1]

An **embolus** is any body transported by the circulating blood, and capable, by reason of its physical characters, of obstructing the flow of blood in any part of the vascular system. As Park states, the essential element is transportation or carriage of some solid or semi-solid body in the circulation. Oil and air, while not solid bodies, may be impacted within the capillaries, and hence may constitute emboli. The transportation and lodgment of emboli and in part, at least, the resulting changes constitute the process of **embolism.** Emboli are usually too large to pass the capillaries. They may be composed of: (1) Thrombi detached or in fragments. (2) Fragments of the cardiac valves or endocardial vegetations; the latter truly thrombi. (3) Calcareous plaques. (4) Fragments of morbid growths torn from tumor masses that have penetrated a vessel wall. (5) Purely extraneous bodies, such as bubbles of air, pieces of bone, or oil globules that may have gained ingress as a result of fracture or injury to bone; extensive laceration of adipose tissue may also give rise to oil embolism. According to Connell, there are about 250 cases of fat embolism on record. It has followed subcutaneous injection of oil and paraffin. The most common cause is fracture of bone. Engel has seen fat embolism of the lung follow hepatic injury. The writer had an opportunity to observe a death from fat embolism following excision of the mamma for carcinoma; the patient was an unusually obese woman, fifty years of age. As a result of trauma, not only fat but fragments of tissue may enter the circulation; laceration of hepatic tissues may result in the displacement of fragments that, later, may be recognized in pulmonary infarcts. Schlöffer records instances in which bullets entering the heart or great

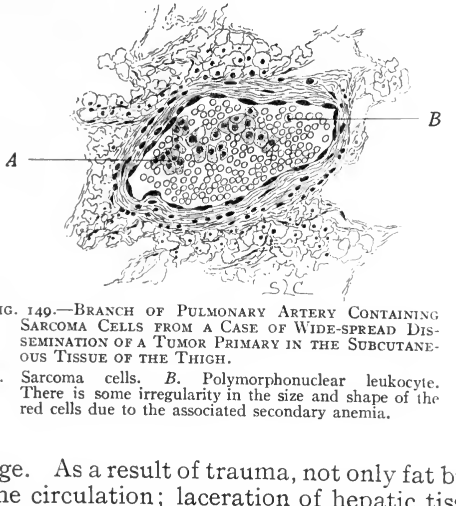


FIG. 149.—BRANCH OF PULMONARY ARTERY CONTAINING SARCOMA CELLS FROM A CASE OF WIDE-SPREAD DISSEMINATION OF A TUMOR PRIMARY IN THE SUBCUTANEOUS TISSUE OF THE THIGH.

A. Sarcoma cells. *B.* Polymorphonuclear leukocyte. There is some irregularity in the size and shape of the red cells due to the associated secondary anemia.

[1] Miller, "Amer. Med.," Aug. 2, 1902. De Groube, "Revue de Chir.," 1895, vol. xv. MacCallum, "Amer. Med.," March 21, 1903, p. 452. Riethus, "Deut. Zeit. f. Chir.," Bd. 167. Schlöffer, "Beitr. zur klin. Med.," vol. xxxvii, No. 3. Engel, "Münch. med. Woch.," June 25, 1901. Claisse and Abrami, "Soc. méd. des Hôp.," April 14, 1905. Gevele, "Beitr. zur klin. Chir.," 1904, Bd. 43, H. 2. Robinson, "Med. Record," Jan. 14, 1905. Greene, "Amer. Jour. of Med. Sci.," Dec., 1904. Dearborn, "Annals of Gynecology and Pediatry," Boston, November, 1904. Richter, "Arch. f. Gyn.," 1904, vol. 74, No. 1. Oswald, "Zeit. f. klin. Med.," 1904, Bd. 53. De Quervain, "La Semaine Médicale," 1904, xiv, No. 41. Moynihan and Dobson, "Practitioner," Oct., 1904, p. 538. Schlöffer, "Zeit. zur klin. Chir.," Bd. 37. Fibiger, "Nordiskt Mediciniskt Arkiv" (Stockholm), March 10, 1900. Hödlmoser, "Zeit. f. Heilkunde," 1904, Bd. xxv, H. 5, p. 109. Connell, Amer. Med. Assoc., Section in Surgery, June 10, 1904. Wolf, "Virch. Arch.," Dec. 1, 1903, Bd. 174, p. 454. Welch, "Allbutt and Rolleston, System of Med.," vol. vi.

vessels have been carried along with the blood-stream, and have occluded vessels. (6) Certain parasites, such as the echinococcus, filaria, etc., are transported by the circulating blood.

Thrombi or emboli are sometimes spoken of as (1) *arterial*, (2) *venous*, or (3) *capillary;* multiple; miliary; traumatic; neoplastic, arising from tumors; specific and nonspecific; simple and malignant: these terms require no further definition.

Occasionally, an embolus arising in the venous system passes directly from the right to the left side of the heart, through a defect in the septum between the auricles or ventricles, in which case it is spoken of as a **paradoxic** or **crossed embolus.** In very rare instances, as a result of sudden alterations in the blood-pressure affecting only one area, emboli may float backward in the venous stream, producing what is known as **recurrent embolism,** or they are called **retrograde emboli.** This was, at one time, assumed to explain certain abscesses of the liver, which are now known to be due to emboli arising in the portal system.

The most important classification of emboli is the division into **simple** and **infective,** the terms having the same meaning as already given when considering thrombi.

Changes Induced by an Embolus.—An embolus floats along in the blood-stream until it reaches the bifurcation of a blood-vessel either branch of which is too small to transmit the mass, or until it enters a vessel the progressive narrowing of which soon leads to its impaction; it obstructs or arrests the stream, and commonly leads to the formation of a thrombus; the blood-supply transmitted by the occluded vessel is arrested, and the area beyond suffers from the altered circulatory conditions. The changes that take place in the affected area vary in degree, and are greatly influenced by a number of factors, among which may be mentioned the character and size of the embolus, the functional importance of the tissue involved, the presence or absence of an abundant collateral circulation, and the possibility of secondary infection or of a primary infection in a simple necrotic area. With regard to the character and size of the embolus, it may be said that, as a rule, massive emboli, such as dislodged thrombi of considerable size, are likely to obstruct the circulation of an area that may be sufficiently large at once to induce alarming symptoms or immediately fatal results. Thus, emboli of considerable size thrust into the pulmonary artery may lead to almost instantaneous death. For the production of this result it is not necessary that the circulatory arrest be dependent upon the occlusion of a large trunk; the scattering of a considerable number of small emboli (an *embolic shower*) brings about exactly the same result. The shape of an embolus may be such as only partly to obstruct a blood-vessel, and therefore not at once to cut off nutrition to the area beyond. Soft emboli plug vessels more completely than the more solid ones, which do not so readily mold themselves to the vessel lumen.

The functional importance of the tissue involved scarcely merits more than mere mention. Thus, it will be evident that a small embolus involving cutaneous, subcutaneous, or allied structures may induce so little change as to escape detection, while an embolus of the same size involving either the coronary artery or a cerebral area presiding over functions of great importance might, in either case, cause immediate death. The suddenness with which symptoms manifest themselves is

also, to a certain extent, dependent upon the importance of the tissue involved. The possibility of at once establishing sufficient collateral circulation to supply nutrition to the area determines, to a large extent, the character of the subsequent changes. With the sudden stoppage of circulation the distal portion of the artery empties itself of blood, and an area of ischemia is thereby induced. The sudden and persistent diminution in the intracapillary pressure favors the influx of

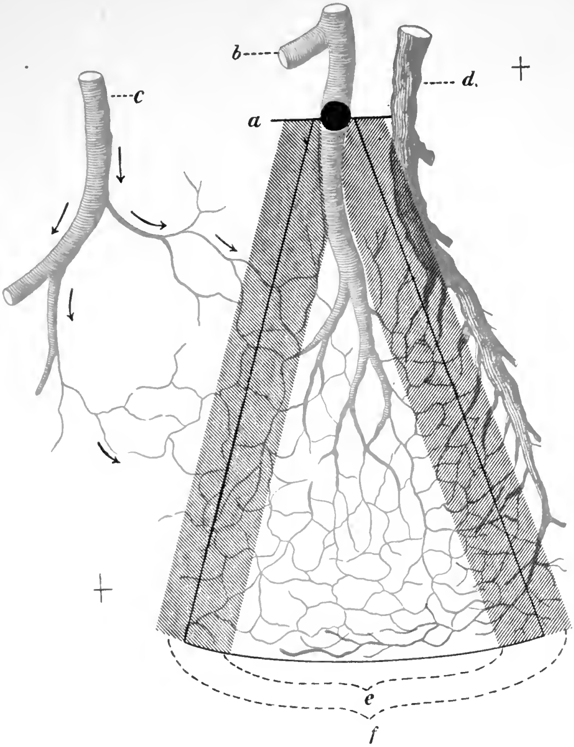


FIG. 150.—SCHEME ILLUSTRATING THE FORMATION OF AN ANEMIC INFARCT BY OBSTRUCTION OF A TERMINA ARTERY.—(*Chantemesse and Podwyssotsky.*)

a, Embolus occluding artery. *b*, Branch of trunk given off above embolus. *c*, Artery of small caliber supplying the tissues adjacent to those nourished by the occluded artery, with the capillaries of which there is scanty anastomosis. *d*, Vein draining the affected area. The bracket from the letter *e* indicates boundaries of the anemic or white infarct. *f*, Zone lying between the anemic infarct and adjacent tissue; in the outer margin of this area the process of repair is inaugurated, or, if the infarct has been due to an infected embolus, it is at this point that the contest between infection and living tissues will be most active.

blood from adjacent capillaries whose contained blood is, as a matter of course, directed in the line of least resistance. Coincident with the changes just mentioned dilatation of anastomosing or collateral arteries occurs, increasing the amount of blood traveling through those vessels. When the anastomosis between the artery involved and the arteries whose circulation still remains intact is sufficiently free, there is quickly formed a circulation adequate to maintain the nutrition in the previ-

ously ischemic area. With the establishment of sufficient collateral circulation the nutrition and function of the area may be resumed, while the changes that take place in the lodged embolus may be practically those already considered when discussing the changes to which a thrombus is liable.

In the absence of a sufficient circulation in the area, degenerative or necrotic processes occur. In the brain, in the spleen, and, to a

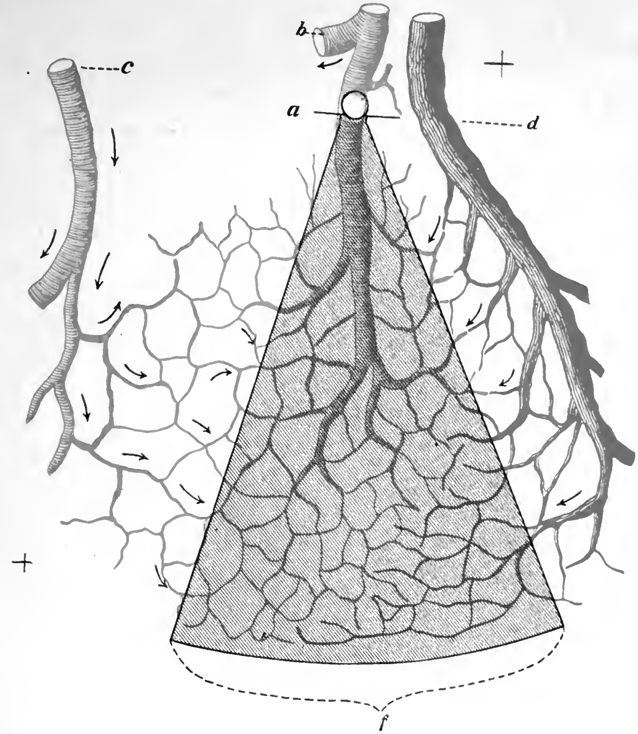


FIG. 151.—SCHEME ILLUSTRATING THE FORMATION OF A HEMORRHAGIC INFARCT AS A RESULT OF OBSTRUCTION IN A TERMINAL ARTERY.—(*Chantemesse and Podwyssotsky.*)

a, Embolus occluding the artery. *b*, Branch of artery given off above embolus. *c*, Artery supplying part of the contiguous tissue, the capillaries of which are continuous with those of the occluded vessel. *d*, Vein draining the affected area; as a result of the arterial occlusion and fall of pressure in the branches supplied by the plugged artery there may be a slight afflux of blood from the vein, as indicated by the arrows on the right. *f*, Base of conical infarct which on section is wedge-shaped.

certain extent, in the kidney, there is not, beyond a given point, a liberal anastomosis between the blood-vessels of adjacent areas. Such blood-vessels are said to be *terminal;* this implies that the tree-like branches given off by one vascular stem do not communicate freely with similar branches of adjacent vessels. The plugging of such vessels is followed by death (necrosis) of the area involved, which is now called an **infarct.** When the area remains ischemic (**anemic** or **white infarct**),

the uncomplicated necrotic process presents the changes already described when considering coagulation necrosis. The area is wedge-shaped on section—truly cone-shaped, with the apex of the cone corre-

FIG. 152.—PART OF SPLEEN THE SEAT OF MULTIPLE ANEMIC INFARCTS.

sponding to the point of embolic obstruction and the base directed toward the surface of the organ. This typical cone shape is greatly modified by the presence of even a moderate degree of anastomosis

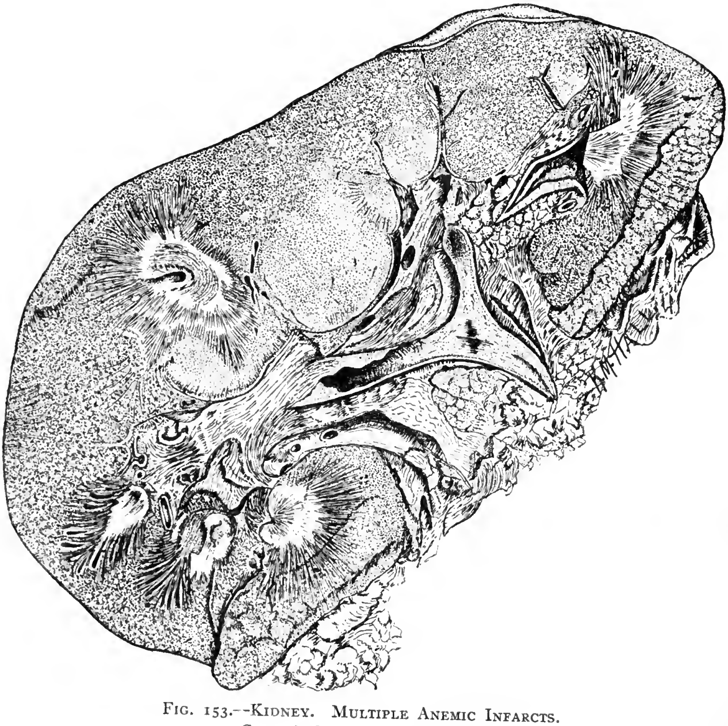


FIG. 153.—KIDNEY. MULTIPLE ANEMIC INFARCTS.
Case of ulcerative endocarditis.

at the periphery, and in large infarcts, or when multiple infarcts join, it may not be present. The consistence of the tissue is dependent upon the amount of coagulable material present. When the necrotic

area has been infiltrated with lymph from the adjacent tissue, the swelling and increased density may be conspicuous. If the area be very large, the center may undergo fatty degeneration (probably liquefaction necrosis, or it may be autolysis) and may soften, converting it into a cyst; when liquefaction necrosis has followed the coagulative processes, the fluid can be absorbed and cicatrization may ensue. When the area is smaller, repair not uncommonly takes place. Proliferation of the connective-tissue elements occurs, resulting in the production of embryonic tissue and finally in cicatrization; into this lime salts may be infiltrated.

During the progress of the necrotic processes the resistance of the tissue to infection is greatly reduced, and not infrequently an infarct, resulting from a simple embolus, may develop suppuration. If the necrosis is so situated as to offer favorable opportunities for infection, the chances of its occurrence are greatly increased.

The foregoing description applies to the anemic infarct and to the process spoken of as *anemic infarction*. In some instances, after a varying period of anemia the capillaries of an ischemic area become overdistended with blood, admitted, for the most part, through adjacent communicating capillaries, or, slightly, if at all, by venous regurgitation; from the congested capillaries extravasation of blood into the connective tissue occurs, and, in addition to the coagulation necrosis in progress in the cellular elements of the area, a further fibrinous matting together results from the associated hemorrhagic infiltration. The resulting change constitutes a **hemorrhagic infarct,** and the process terminating in its formation is known as *hemorrhagic infarction*. The shape of the area is not altered by the occurrence of hemorrhagic infiltration. The swelling, however, is more marked; the color is dark red, at times almost black; and the density is greatly increased by the presence of the coagulated blood. The subsequent changes are the same as those occurring in areas of anemic infarction.

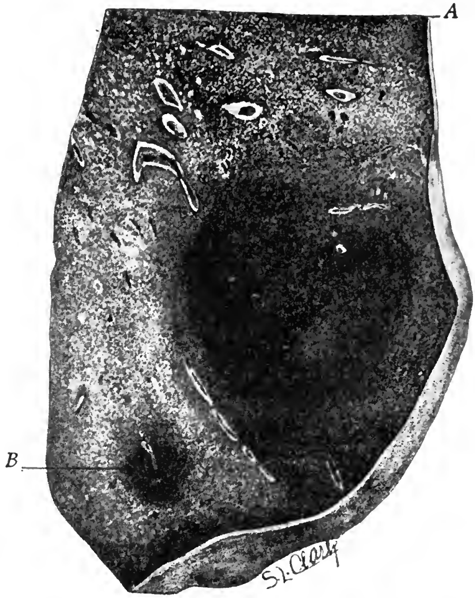


FIG. 154.—LUNG, HEMORRHAGIC INFARCT (NATURAL SIZE). *A*. Pleura. *B*. Small infarct centrally placed. The large infarct shows the elevation of the pleura, the hemorrhagic suffusion of the central area, and the periphery of inflammatory hyperemia.

It has been held that an anemic or white infarct is but a later stage of the hemorrhagic form and that it is dependent upon the removal of the blood coloring-matter from the latter. It is possible that such

a change occurs, and that the results of the two processes may be the same; but certain infarcts are clearly anemic from the beginning, and others are hemorrhagic early in their development.

The changes revealed by the histologic examination of the necrotic tissue will not be exactly the same in different stages of the process. They are practically those already mentioned when considering coagulation necrosis. (See p. 251.)

In emboli containing bacteria (infective emboli), and in those containing the specific cellular elements of tumors (neoplastic emboli), arrest is followed by the development of the morbid process whose etiologic factor they transmit. If the embolus contains pyogenic organisms, an abscess is engendered; by reason of the constant presence of these abscesses in pyemia, they have long been known as **pyemic abscesses.** By reason of the fact that such abscesses appeared to change their location, they were called **metastatic abscesses.** Emboli containing tubercle bacilli induce tuberculosis at their point of lodgment. It is probable that *amebic abscesses* in the liver arise as the result of emboli containing amebæ brought from the intestinal lesion. A tumor infiltrating the wall of a blood-vessel, particularly a vein, may have swept into the circulation small fragments that projected into the blood-stream, and these, in turn, arrested in the distant capillary, may resume their growth and give rise to a secondary tumor nodule, or *metastatic growth.* From the infected, parasitic, and neoplastic emboli secondary thrombi may form, from which, again, additional emboli may be broken off to continue the process of dissemination.

When deposited upon the septa of bifurcating vessels, orifices of branches, or other suitable points, emboli containing bacteria may, by inducing an infective endarteritis, give rise to softening of the vessel wall and finally ectasia,—a condition called **embolomycotic aneurysm.**[1]

[1] Lewis and Schrager, "Jour. Amer. Med. Assoc., Nov. 27, 1909.

CHAPTER XI.

INFLAMMATION AND REPAIR.

INFLAMMATION.[1]

Probably the most acceptable definition of inflammation is that given by Park, which is, as he states, a modification of one suggested by Sutton: "Inflammation is an expression of the effort made by a given organism to rid itself of or to render inert noxious irritants arising from within or introduced from without." It is probable that inflammation represents the process of repair plus (1) infection or (2) the removal of dead tissue, a relationship to be further brought out when considering the causes of inflammation.

Etiology—As just indicated, inflammation is ordinarily produced by irritation or injury. The forms that these factors may assume are manifold, and any attempt to enumerate the various etiologic elements leading to inflammatory manifestations would lead far beyond the contemplated scope of the present article. The surgical tendency to consider inflammation as always the result of infection can scarcely be considered justifiable. After all, infection acts only by destroying the cells or irritating them by the noxious products of bacteria. It is true that bacteria are the most frequent irritants, and that a large percentage of the inflammatory processes arises as a result of bacterial activity. Bacteria or their products destroy or irritate the cells, and manifest a peculiar action upon the fixed and migratory cells of the economy, thereby inducing inflammatory processes more or less constant for each particular species of organism. The activity of the inflammatory processes induced by bacteria depends upon one of two factors: (1) the pathogenic power of the germ in question; (2) the degree of susceptibility of the tissues. As an example of the first condition it will be noted that if the two ears of a rabbit be inoculated with the anthrax bacillus or with the streptococcus pyogenes, using germs that are somewhat attenuated in one ear, and a more virulent organism for the other, there will be a decided difference in the local reaction as manifested in the two organs. Many experiments conducted along this line have led to conclusive proof that the pathogenicity determines to a large degree the activity of the ensuing inflammatory process. The importance of the second factor in the production of

[1] For a full comprehension of inflammation every student should read Metchnikoff, "Comparative Pathology of Inflammation" (English translation), 1893. Adami, "Allbutt's System of Med.," 1898, vol. i, p. 54. Bonney, "Middlesex Hosp. Jour.," June, 1904, p. 101. Chantemesse and Podwyssotsky, "Les Processus Généraux," 1905, vol. ii, p. 333, bibliography, p. 407. Walker, "General Pathology of Inflammation, Infection and Fever," London, 1904. Baumgarten, "Berlin. klin. Woch.," Oct. 1, 1900. Monti, "Fundamental Data of Modern Pathology," 1900. From these the older literature can readily be followed.

inflammation is equally well established. The susceptibility of the tissues may be augmented by reduced vitality, associated irritation, by the absence of immunity, either inherited or acquired, and by circulatory disturbances, or certain perversions of the nervous system. The susceptibility of an animal to a given infection undoubtedly varies at different times—a fact well shown by the occurrence of severe inflammatory processes after most trifling injuries, which, under other conditions, apparently give rise to little disturbance.

Injury to the tissue, whether it be mechanical, chemic, or thermal, is followed by the occurrence of the phenomena of inflammation; the extent and severity of the inflammatory process are dependent upon a number of associated factors. As just indicated, infection truly represents a chemic injury to the tissue, the noxious irritant being the specific product of the infecting organism. Inflammation may be induced by the injection of bacterial products without the presence of bacteria. Here the tissues are dealing with chemic bodies alone As further evidence of the phlogistic power possessed by chemic bodies may be cited the inflammation induced by the subcutaneous introduction of calomel, turpentine, croton oil, and similar irritants. That such inflammations are not purely of experimental production is established by their occurrence after the use of powerful antiseptics in too concentrated a form. There can be no doubt that the abundant use of mercurial solutions in wounds—a frequent procedure in early antiseptic surgery—led to necrosis of a large number of cells and to the occurrence of a certain degree of inflammation. Recognizing this, surgeons have adopted asepsis whenever possible. Even in infected areas abundant flushing with sterile fluids has been found to be attended with less local reaction than the use of even mild antiseptics. In a comparatively frequent form of conjunctival inflammation in the new-born, evidently the cause has not been the microorganism usually present (gonococcus), but the vigorous use of agents directed toward its destruction. In this instance and in those previously given the inflammation arises as the result of cell destruction brought about by agents directed toward the prevention of infection or toward the removal of existing organisms. The destruction of tissue and the production of exudates by chemic agents is further illustrated by the tissue reactions resulting from the application of so-called counter-irritants, such as mustard, cantharides, turpentine, and chloroform, all of which induce an inflammatory response. Wounds of all kinds involve destruction of a varying number of cells and injury to others. The wound made by the sharpest instrument is marginated by a layer of lacerated cells. The more extensive the wound, the greater the number of cellular elements involved; and, of course, injuries made by dull, tearing, vulnerating bodies contain more lacerated cells than wounds of like extent made by sharp, clean-cutting instruments.

It will be observed that the whole list of inflammatory causes embraces at every turn the destruction of cells. The destroyed cells at once become irritants and induce inflammation in the adjacent viable tissues. The simple aseptic inflammatory reactions differ from the septic, in that the latter contain destructive agents that are constantly increasing, and, hence, the inflammatory processes seen in wounds, made under aseptic conditions, are but trifling as compared

with the extensive inflammations following destruction of tissue associated with the introduction of infective agents that themselves further extend the cell necrosis and actively antagonize the process of repair. For this reason the surgeon has been led to regard repair as dissociated from inflammation, and to say that aseptic wounds heal without inflammatory phenomena. The pathologist must, however, recognize that all tissue injuries are attended by a certain amount of cell destruction, and that the effort made by the tissues to rid themselves of the dead elements constitutes, in a certain way, a part of the reparative process. Still, with this admission before us, it is necessary to remember that the essential phenomena of inflammation and the essential phenomena of repair are, to a certain extent, dissimilar. Inflammation is attended by cell necrosis and degeneration; and repair by cell proliferation and regeneration. The possible admixture of the two processes can not be gainsaid. Of course, the same cellular elements at a given point are not evincing both processes, but one may be in close proximity to the other. The periphery of an inflammatory area nearly always shows, in the absence of rapid extension, a marginal zone of reparative effort. Were the effort at repair to remain quiescent until inflammation had terminated, repair would probably become an impossibility.

Morbid Anatomy.—The lesions to be studied in inflammation are: (1) The changes in the blood-vessels; (2) intravascular changes, or those occurring in the vessel contents; and (3) changes in the perivascular tissues.

Changes in the Blood-vessels.—These can be observed in any vascular, transparent membrane, such as the tongue, mesentery, or web of the hind foot of a frog or the mesentery of a suitable warm-blooded animal. If such transparent tissues be so arranged as to permit of their examination under the microscope, the following changes can be observed:

At the beginning of the examination the normal capillary presents itself as a transparent tubule, within which can be seen the circulating blood. As a rule, the application of an irritant is not necessary; exposure to the air, with the associated trauma incident to the arrangement of the tissue, will usually bring about the modifications to be observed. In other instances, as in the web of a frog's foot, it may be necessary to snip off with the scissors a thin layer of the epithelial covering, carefully avoiding any wound to the underlying blood-vessels. The blood-vessels at once contract, and at the same time the current is markedly accelerated; this phenomenon is of brief duration, often persisting but a moment, and within the first hour after the injury the brief period of contraction will be followed by beginning dilatation. At first the dilatation is regular; it then becomes varicose, and, in more marked cases, saccular projections of the capillary wall may be observed. Capillaries at first not recognizable, or at least not transmitting blood, dilate and become more or less distended. A similar dilatation of the arterioles, and particularly of the venules, is also seen. The changes so far observed are probably due to increased capillary tension and to the influence of the noxious agents directly upon the vessel wall. The rise in capillary tension is probably brought about by relaxation of the arterioles through which the blood-supply to the part is admitted. The increased amount of blood present in the area is

evident to the unaided eye. It is not possible at this stage to recognize any structural alterations in the cells that compose the capillary wall, nor are we able to see any enlargement of the capillary stomata, or any separation of the endothelial plates. A study of properly fixed preparations usually shows that the endothelial cells are swollen, and, when the process has lasted for any length of time, there is not uncommonly evidence of degeneration or proliferation, depending upon the activity of the noxious agent.

Changes in the Blood and Blood-current; Intravascular Changes.—Before the manifestation of inflammatory phenomena the stream within the capillary can be seen to be composed of two parts: (*a*) An *axial stream*, composed of the corpuscular elements of the blood, and therefore spoken of as the *corpuscular stream;* (*b*) a *circumferential* or *parietal stream*, composed of blood-plasma, and hence called the *plasmatic stream.* During the period of acceleration—a period that corresponds to the contraction and beginning dilatation of the capillaries—these two clearly differentiated divisions of the capillary contents are easily recognized. With further dilatation and beginning slowing of the current the axial stream widens and the plasmatic stream grows correspondingly thinner. Within the first hour or so the narrowing of the plasmatic stream becomes marked, and instead of remaining clear, it contains a progressively increasing number of leukocytes.[1] At first these leukocytes roll along the vessel wall; later, they become attached at some point and hang off into the slowing stream as pear-shaped bodies, the small end of the pear corresponding to the point of attachment. The margination of the leukocytes is conspicuous in the small veins, but the size of even the larger dilated capillaries does not render the demonstration easy. As the dilatation of the blood-vessel becomes more marked there is poured out into the perivascular tissues a fluid derived from blood-plasma; this fluid constitutes the liquid exudate. Along with this, certain of the leukocytes, as the result of their ameboid movement, pass through the vessel wall and reach the perivascular tissues. During the dilatation of the blood-vessel the blood-current becomes slower and slower, the corpuscles manifesting a slight progression only with each heart-beat, and eventually the collected mass of cells oscillates in the capillary lumen; finally, this oscillation is arrested, and stasis or stagnation occurs. Before this final stage the differentiation into the axial and peripheral streams has disappeared, and the cellular contents of the vessel appear to occupy the entire lumen. With the occurrence of stasis the red corpuscles at points arrange themselves in columns composed of cells piled upon one another like superimposed coins (rouleaux). Migration of the leukocytes continues, and many of these cells present in the stagnant blood move toward the periphery and eventually reach the perivascular tissues. In properly fixed specimens the leukocytes can be seen in various stages of diapedesis. At first a pseudopod is projected through the capillary wall, appearing on the exterior as a small, roundish, knob-like protuberance. The extravascular portion of the

[1]Before attempting to follow the various steps of migration and the functions of the leukocytes in inflammatory and reparative processes, the student is advised to familiarize himself with the table describing and differentiating the leukocytes. (See Chapter I, of Part III.)

cell increases in size by the more fluid protoplasm flowing through the narrowed portion into the extravascular projection. Finally, the nucleus passes through, and apparently the solution in the continuity of the vessel wall disappears. (See Fig. 155.) After the migration of the leukocytes and the lessening of the intracapillary tension by the pouring-out of the exudate, resumption of circulation may be at times observed.

To a certain extent the character of the irritant determines the form of leukocyte most abundant in the exudate. In many of the infections, and particularly in pyogenic infection, the polymorphonuclear leukocyte (finely granular oxyphile cell or microphagocyte) is abundant. In other inflammatory conditions the hyaline cell (macrophagocyte) is most numerous. The most numerous cell may be the small mononuclear, or lymphocyte; rarely eosinophiles are present in any considerable number. Exactly what factors determine the occurrence of one or the other of these cells has not been definitely ascertained. It would seem, however, that in the more acute, and particularly in the suppurative, inflammatory conditions, as already stated, the microphagocyte is the cell that responds to the chemotactic influence exerted by the irritant; in the more chronic lesions, with less active irritants, the macrophagocyte is in excess. It is not possible to affirm, however, with any degree of definiteness, in the present stage of our knowledge, exactly what conditions determine the presence of one or the other of these phagocytes.

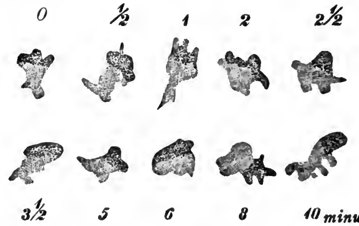


Fig. 155.—Leukocytes of a Frog.—(*Stöhr.*) × 560 diameters.

Extending out from the side of the leukocyte will be seen a number of projections, called pseudopods. In the diapedesis or migration of the leukocyte through a blood-vessel wall in inflammation these pseudopods are first thrust through the wall, the cytoplasm of the leukocyte flowing through into the pseudopod, carrying with it the nucleus, thereby delivering the cell upon the outer side of a blood-vessel wall.

As to the causes leading to the occurrence of migration and to the development of the exudate, two views have been held. It was long maintained that it was purely a physical process; the increased vascular tension, with the associated alterations in the capillary wall, led to the escape of part of the fluid contents of the vessel. By this theory the vessel wall was presumed to be passive. Later investigations have led to the adoption of an entirely different opinion. Under the older view it was believed that the fluid normally present in the lymph-spaces of the various tissues was filtered through the vessel wall as a result of the intravascular tension. Later observers hold that the endothelium of the capillary secretes this fluid, and that instead of being a transudate, as originally thought, it is purely a secretory product of the endothelium. Admitting the correctness of this view, the material that we have been considering as an exudate must now be regarded as, at least in part, a secretion. The technical difficulties that attend efforts to demonstrate the correctness of either theory have been so great that neither is at present deemed fully acceptable. The theory that the migration of the leukocytes is dependent upon increased vascular tension can not, of course, be maintained, as wandering cells

already present in the tissues adjacent to an inflammatory area show migration toward the center in spite of the fact that such migration must be in the direction of the point of greatest pressure.

Changes in the Perivascular Tissue.—In the perivascular tissues two distinct classes of elements must be considered: (1) Changes occurring in the elements normally present; (2) changes that follow in the fluids and cells coming from within the vessels. It has been stated, and apparently correctly, that changes occurring in the normal perivascular structures are essentially the same as those seen in tissues that are normally avascular. As a type of such tissue, the cornea may be studied. The corneal tissue is abundantly supplied with lymph-channels, but contains absolutely no blood-vessels. The lymph circulating through the corneal lymph-spaces is derived from the capillary circulation surrounding the organ. Destruction of a small, superficially placed central area of the cornea by means of chemic irritants, or the removal of a thin superficial layer is followed by opacity at the point of injury, extending as a zone of haziness for some distance beyond. The preliminary degenerative changes in the corneal corpuscles are quickly followed by reparative efforts. Leukocytes surround and eventually infiltrate the area, while the undestroyed connective-tissue cells (corneal corpuscles) begin to show evidence of proliferation. The proliferative changes in the corneal corpuscles are evidently the initial steps in the process of repair. The leukocytes present in the area could not have arisen as a result of increased pressure directed toward the point of injury, but must be present as the result of some other factor. This leads us to discuss causes inducing the evident migration of leukocytes toward the area of injury.

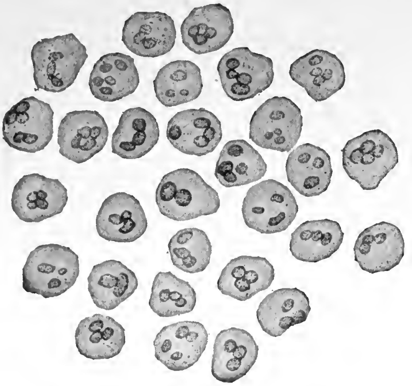


Fig. 156.
Polymorphonuclear leukocytes from center of one of the infiltrated areas in a section of the cerebral cortex and meninges from a case of suppurative meningitis. Section stained with toluidin-blue.[1] (Zeiss $\frac{1}{12}$-inch oil immersion; Queen oc. B.)

Fig. 157.
Mononuclear cells from meninges in a case of tuberculous meningitis. Section stained with toluidin-blue. (Zeiss $\frac{1}{12}$-inch oil immersion; Queen oc. B.)

De Bary observed that certain plasmodia moved toward the nutritive material placed in their vicinity, and a further study showed that at least three classes of substances could be recognized: (1) Substances toward which the plasmodia moved; (2) substances that did not seem to influence the

[1] The microscopic drawing made from this section will be found in the chapter on Diseases of the Nervous System, under the head of Suppurative Meningitis.

organism; (3) substances from which the organism receded. This property of cellular attraction and repulsion is called **chemotaxis,** or **chemiotaxis.** When the cell is evidently drawn toward the body, the condition is called *positive chemotaxis;* when repelled, *negative chemotaxis.* Positive chemotaxis is admitted. Negative chemotaxis interests us but little; the existence of such a condition has been doubted, although experimental evidence would indicate its occasional occurrence. Experiments show that leukocytes travel toward certain infecting bodies, and that dead tissue is apparently attacked by these cells. The ultimate explanation of chemotaxis is still wanting; we do not know whether it is a chemic affinity or a phenomenon allied to diffusion in simpler bodies, or whether it is an essential characteristic of certain cells not dependent on known chemic and physical explanations applicable under what seem to be similar circumstances.

The cells influenced by positive chemotaxis arrive at the area of irritation from two directions: from the blood-vessels the polymorphonuclear leukocytes migrate in large numbers, while from the same source and also from the adjacent connective-tissue spaces come the large hyaline cells and eosinophiles. Eventually, the field of observation becomes so clouded by the cellular elements present that continued study of the previously transparent tissue is no longer possible. Whether all the leukocytes present in the area came from the sources just indicated or whether some of them are the result of proliferation has not been definitely determined. It is reasonable to conclude, from data at hand, that a certain number of the leukocytes may result from proliferation of migrated cells. That this number is large, or that proliferation constitutes an important process in the production of the large number of migrating cells present, seems doubtful.

Recent studies of the cells migrating in inflammatory processes show clearly that irritants of different kinds or different intensities of action have each more or less specificity in the manifestation of their chemiotactic power. The pyogenic bacteria attract polymorphonuclear leukocytes; the toxins of the tubercle bacillus, except when in a concentrated form, lead to accumulations of mononuclear cells, and in a general way the same is true of the poison of syphilis. Reference has already been made (p. 207) to the fact that in the presence of certain animal parasites eosinophile leukocytes become unusually numerous in the circulating fluid. A knowledge of these facts has been turned to diagnostic purposes; exudates rich in polymorphonuclear cells may safely be looked upon as due to pyogenic irritants. The presence of mononuclear cells suggests tuberculosis or syphilis. Serous accumulations (transudates) contain no more polymorphonuclear cells than will be found in an equal quantity of fluid from any other part of the body, are also poor in mononuclear leukocytes, but contain numerous endothelial cells derived from the membrane lining the serous cavities or lymph-spaces. Diagnosis by an examination of the cellular content of inflammatory exudates is called **cytodiagnosis.**[1] It has been shown to have

[1] The important clinical aspects of cytodiagnosis are given by Labbé, "Le Cytodiagnostic," Paris, 1903. The following papers may also be consulted: Froin, "C. R. Soc. de Biol.," 1904, p. 1901. Labbé, "La Presse Médicale," Aug. 10, 1904, p. 505. Barjon and Cade, "Arch. Gen. de Méd.," August, 1902, p. 160. Beattie, "Jour. of Path. and Bact.," June, 1902, vol. viii, No. 2. Whitfield, "Brit

considerable value, but its limitations have also been demonstrated. It is well known that tubercle bacilli in unusual numbers or of exceeding virulence lead to suppuration (accumulation of polymorphonuclear leukocytes). The same organisms, however, in numbers commonly found, give rise to the accumulation of mononuclear cells (mononucleosis). Cytodiagnosis has been most used, and the results found the least fallacious, in the examination of exudates in the serous cavities, particularly the meninges, pleura, peritoneum, joints, and tendon-sheaths. It has its advantages, but can not be relied upon implicitly, as was at first believed.

In many conditions the cell most abundant in the exudate is also found increased in the body-fluids, particularly the blood. Polymorphonuclear leukocytosis (polymorphonucleosis) is found in many inflammatory processes, particularly those in which exudates containing large numbers of these cells occur. Diseases due to certain animal parasites are attended by hemal increase in the eosinophiles (eosinophilia). In malaria, syphilis, and sometimes in tuberculosis, the mononuclear cells of the blood are unusually abundant. This feature of infections is further considered in the chapter dealing with the pathology of the blood.[1]

The changes that take place in the fixed cells of the tissues involved, as well as the alterations that the invading cells may undergo, are dependent upon a number of conditions. If the irritant be active,—as, for example, the poison of virulent bacteria,—many of the cells are at once destroyed. When the pathogenicity of the irritant is less marked, degenerative changes may be more conspicuous than actual cell death. The characters and degree of the degenerative and necrotic changes vary in different tissues, and are more marked in organs whose cellular constituents are largely of epithelial origin. In the liver and kidney the degenerative phenomena that attend inflammation may be more conspicuous than the exudate. In such epithelial structures cloudy swelling, fatty degeneration, and hydropic distention of the cells with nuclear fragmentation and necrosis may be conspicuous. In the connective tissues mucoid and hyaline transformation may be present. The amount of degenerative change and the associated cellular disintegration are also dependent upon the intensity of the irritant; such degenerations are most marked in the various infections of which the pyogenic constitutes a typical example.

The fluid exudate now present in the perivascular tissues varies in quantity and composition. The quantity, and to a certain extent, the chemic composition, are dependent upon the character and strength of the irritant as well as upon the tissue involved. The more richly vascular the area, as a rule, the greater the amount of the exudate. Loose connective tissues, such as the eyelid, scrotum, and labia, show marked accumulation of exudative fluids. The same is commonly true of serous membranes, and, to a lesser degree, of the subcutaneous and submucous connective tissues. The fluid differs in chemic composition from the

Jour. of Dermat.," Jan., 1904, p. 7, Feb., 1904, p. 63. Schwarz, "Wien. klin. Woch.," Nov. 3, 1904, p. 1173. Wolff and Torday, "Berlin. klin. Woch.," Dec. 5, 1904. Leuchs, "Virch. Arch.," July 1, 1904, Bd. 177, p. 28. Hektoen and Ruediger, "Jour. of Infectious Diseases," 1905, vol. ii, No. 1, January 12, pp. 128–141. Lewkowicz, "Wien. klin. Woch.," Sept. 15, 1904, p. 979. Miller, "Trans. Chicago Path. Soc.," May 9, 1904, vol. vi, No. 5.

[1] See Leukocytosis and Leukopenia

fluid in edema; its specific gravity is higher (edema, about 1.005 to 1.015, rarely over 1.018; inflammatory exudate, 1.015 to 1.025); it is highly albuminous, not uncommonly containing five times the quantity of proteids present in edema fluids; it is rich in fibrin. When bacteria are present, the fluid usually contains peptone, which, in old suppurative processes or when the lesion is extensive, may enter the general circulation and may be excreted in sufficient quantity to be recognizable in the urine. For evident reasons the inflammatory exudate is rich in cells, an abundance of which may render the fluid quite opaque.

The leukocytes brought into the area by any of the processes indicated at once attack the infecting organism,—if bacteria be the cause of the inflammation,—or proceed to remove the dead tissue when the inflammatory process is associated with, or has arisen secondary to, cellular destruction. The phagocytes active in this process have been mentioned. As already stated, when considering phagocytosis in its connection with immunity, it is not improbable that certain phagocytes liberate antitoxic or bactericidal bodies which exert a certain amount of influence in subduing infection. (See Phagocytosis, p. 98, and Phagolysis, p. 99.)

The fluid portion of the exudate relieves the intravascular tension by its escape, dilutes the irritant present in the tissues, carries with it antitoxic and bactericidal properties, and possibly in some instances affords increased nutrition (?) to the cells of the area. The fibrin-forming bodies contained within the exudate reaching the perivascular tissues give rise to fibrin, which acts not uncommonly as a limiting body, retarding the dissemination of bacteria and lessening the rapidity with which the toxic substances present are diffused into the surrounding tissues. Its function in the repair of wounds will be considered later.

Terminations of the Inflammatory Process.—These are largely dependent upon the activity and persistence of the cause, as well as upon the susceptibility of the tissue, including under this term the activity of the protective agencies whose tendency is always directed toward the arrest of irritant action. When the etiologic factor is readily overcome, or is quickly withdrawn, restitution to the normal may be brought about without leaving any evidence of a past inflammation. In the early stages of the inflammatory process the withdrawal of the cause is quickly followed by absorption of the exudate and the reestablishment of the circulation. The exudate passes off by the lymphatics or is taken up by the veins, and the few extruded leukocytes re-enter the circulation, either directly, through the blood-vessels, or indirectly, through the lymphatics, eventually leaving no recognizable tissue alteration. As the inflammatory process continues, so favorable a termination becomes less and less possible, until finally the tissue alterations are such that a return to the normal is no longer to be anticipated. Under such circumstances the occurrence of repair is the best that can be expected; and the longer such repair is delayed, the less effectual it is likely to be. The most important factor in the prevention of repair is infection; and the more active this infection, the more grave the tissue alterations will be, and the less perfect the subsequent repair.

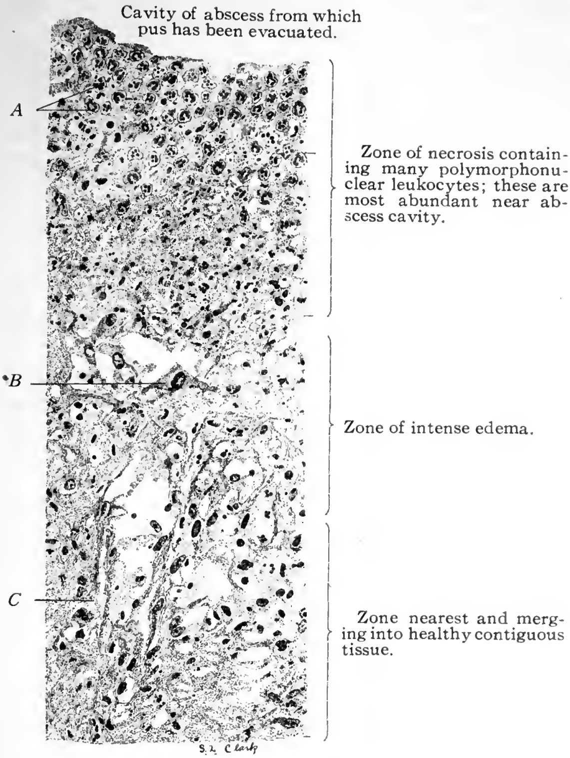
Suppuration.—The organisms most active in the production of

suppuration are the staphylococci and streptococci—pyogenic cocci. While the foregoing are the usual bacteria active in suppurative processes, it is not to be forgotten that many other organisms share this pus-producing power. Thus, the Bacillus coli communis, Bacillus pyogenes fœtidus, Bacillus typhosus, Gonococcus, Micrococcus cereus flavus, Micrococcus cereus albus, Pneumococcus, the fungus of actinomycosis, Bacillus pyocyaneus, Bacillus anthracis, and other organisms, occasionally manifest pyogenic activity. In most instances suppuration is due to mixed or concurrent infection. Commonly, at least two organisms are present, and in many instances a number may be associated. A series of unpublished investigations conducted by Lockett in the writer's laboratory showed that of one hundred consecutive suppurative processes, a single infection was the exception. These observations are corroborative of many similar studies made by other observers.

Abscess.—In infection by pyogenic organisms the continued action of the irritant (a necessary sequence of bacterial proliferation and of the continued production of toxins) prolongs the period of exudation and necrosis and increases the quantity of the exudate, which is particularly rich in phagocytic cells, the most abundant of which is the finely granular oxyphile cell—the polynuclear or polymorphonuclear leukocyte. The bacterial products lead to degenerative and necrotic changes in the fixed tissue elements, associated with liquefaction of the intercellular substance, converting the area so affected into a mass of cellular detritus in which the cell longest retaining its morphologic characteristics—the polymorphonuclear cell, now the pus-corpuscle—is most abundant. It has usually been held that liquefaction of the exudate depended upon the peptonizing influence of bacterial products. It is probable, however, that the softening and subsequent fluidification are due to the activity of products liberated by the cells, especially the leukocytes, and therefore present in the fluids of the affected tissue. In no other way is it possible to account for the abscess formation which results from the introduction of purely chemic irritants. The studies of Rulot[1] and others have demonstrated that the leukocyte contains, and on destruction readily yields, bodies through the action of which fibrin may be liquefied and other so-called autolytic changes produced. The fluid resulting from these changes is called pus.

Pus is a creamy liquid possessing a faint, sweetish odor; its specific gravity ranges between 1.020 and 1.035, with a mean of about 1.032. Essentially, pus is composed of two elements—the fluid and cellular portions. The fluid constituent is called the *liquor puris;* it represents the serous constituents of the exudate, to which has been added the fluid resulting from the liquefaction of the intercellular substance and, possibly, from the dissolution of a number of the tissue elements, and, it may be, of some of the cells. It is comparatively rich in albumoses, to which the absence of coagulability has been attributed. It also contains leucin and tyrosin. Binaghi[2] has demonstrated the bacteriolytic and to a certain extent the antitoxic properties of pus. An animal unusually susceptible to an organism—for example, the anthrax bacillus—may escape if the inoculation be made into a cavity containing pus; subsequent examination of the

[1] "Arch. internat. de Physiol.," t. i, 1904, pp. 152–158.
[2] "Rif. Med.," May 4, 1904.



SECTION OF WALL OF ABSCESS.

A. Polymorphonuclear leukocytes forming, almost alone, the inner stratum. *B*. Resisting connective tissue cell many of which have disappeared. *C*. Residual fibers of connective tissue. The arbitrary zones indicated on the right are rarely, if ever, clearly defined.

fluid shows that many of the organisms have disappeared. That the substances antagonizing the bacteria are present in the pus and not in the body-fluids—at least, in the same quantity—is indicated by the fact that the same animal may readily be infected by inoculation through paths that do not bring the microbe in contact with the pus. The pus-cell is richly granular, usually polynuclear or polymorphonuclear, and for a brief period following its removal from the body may manifest well-marked ameboid movements; in its present form it can not be differentiated from the polymorphonuclear or finely granular oxyphile cell, which earlier reached the inflammatory field from the blood-vessel. The experiments of Muir show that a cubic millimeter of pus may contain a million leukocytes; if this proportion is maintained, thirty cubic centimeters (one ounce) would contain as many leukocytes as three and a half liters (120 ounces) of blood. The fact that during the evolution of an abscess the number of leukocytes in the blood not infrequently undergoes a constant increase indicates the enormous leukocyte-producing capacity of the body-tissues. With regard to the hyaline or mononuclear cell, occasionally present in pus, our information is less satisfactory; the tendency at present is to regard these cells as invaders from the adjacent connective-tissue spaces—in other words, they are believed to be celomic wandering cells; that they are also derived from the circulating blood seems equally established.

In the production of an abscess, liquefaction first takes place at the center of irritant action, from which, as we pass outward, toward the surrounding uninvolved tissue, all intermediate stages of the inflammatory process may be recognized. The *wall of the abscess* is, therefore, composed of the normal tissues of the part, showing various degrees of inflammatory infiltration, degeneration, and necrosis. The zone lying nearest to the pus is composed of necrotic tissue rich in leukocytes. Surrounding this will usually be seen a zone containing the exudative fluids and numerous white blood-cells. There is usually present more or less fibrin entangled among the fixed connective-tissue fibrils and cells, the latter not uncommonly showing proliferative changes. In this zone efforts at repair and at the prevention of dissemination may be evident. Externally, this zone gradually fades into the normal tissue, and internally it is continuous with the necrotic zone to which reference has already been made. If undisturbed, the abscess tends to travel along the path of least resistance; as the infective agents manifest a disposition to extend in all directions, but are met by the protective forces of the tissues, the path of least resistance must be through those tissues where the protective agencies are least active. The vascularity of the part, and hence the richness in leukocytes, usually results in the extension of the abscess toward the surface, through which it eventually ruptures and discharges its contents. Relieved of this tension, the direction of the fluid exudate is now strongly toward the abscess cavity. This results in flushing out the surrounding lymph-spaces, and favors the action of the protective forces—the phagocytes, antitoxic and bactericidal bodies present in the inflammatory area. When the infective organisms are destroyed or rendered inert, the liquefaction necrosis, leukocyte migration, and consequent formation of pus cease; after incision and evacuation the walls of the abscess collapse, and reparative efforts become ascendant.

Ulceration.—The younger Gross often spoke of an abscess as a subcutaneous ulcer, and in the present state of our knowledge many ulcers could, with propriety, be called superficial or, more correctly, exposed abscesses. Where suppurative processes are so situated that a wall is formed on but one side,—in other words, are exposed,—the floor of the ulcer is structurally quite like the wall of an abscess. This applies, of course, only to ulcers in which infection is active. Exposed or denuded subcutaneous tissues where the removal of the overlying structures has been brought about under strict aseptic precautions bear little resemblance to the changes observed in the formative stage of an abscess. When, however, the ulcer has resulted from infective processes, giving rise to necrosis of the overlying structures, the early stages of ulcer formation are practically identical with those seen in the wall of a developing abscess. The pus formed by such ulcers finds ready egress, and the protective powers of the underlying tissues usually limit and arrest the spread of the ulcerative lesion. Occasionally, however, ulcers show continued necrosis, gradually extending in one or more directions, thereby indicating the inefficiency of the protective powers in the adjacent tissues, or extreme virulence on the part of the infecting organisms; in such cases mixed infection is the rule. The fact that such ulcers appear to extend in one or more directions, as though something were eating away the tissues, led to their being called *phagedenic*.

In addition to abscess formation and ulceration, there are allied forms of infection in which the anatomic peculiarities of the tissues involved, or the absence of resistance, or the intensely toxic power of the infection, give rise to changes resembling abscess formation, but by no means identical. Closely allied to abscess formation is the occurrence of suppurative lesions of the serous membranes. Here the collection of pus takes place in the serous cavity, and is not usually referred to as an abscess.[1] Suppurative processes leading to the accumulation of pus in cavities lined by epithelium occur. As in serous cavities, these are not usually referred to as abscesses; thus, a purulent accumulation in the pelvis of the kidney is spoken of as "pyonephrosis," and in the Fallopian tube purulent distention is called "pyosalpinx."

At times the extension of infection proceeds with such rapidity that a distinct accumulation of pus may not be evident. Thus, in inflammation of the cellular tissues, and in inflammation of the lymph-vessels (angioleucitis) due to virulent infection or to greatly reduced resistance on the part of the individual, the inflammatory process may extend with remarkable rapidity, and may even terminate fatally before the occurrence of any recognizable purulent collection. Sometimes along the paths of such rapidly spreading infections a variable quantity of macroscopically recognizable pus may be developed. Such a condition is usually referred to as *diffuse suppuration*, *suppuration of the cellular tissues*, *purulent infiltration*, *suppurative cellulitis*, and, without any apparent reason, is sometimes called *purulent suffusion*.

The occurrence of gangrene as a result of infection has already been considered.[2]

[1] For the description of suppurative inflammation of serous membranes, see Disease of Serous Membranes, Part III.

[2] See Spreading Gangrene, p. 256.

The terms *acute*, *subacute*, and *chronic*, as applied to inflammatory processes, are used to indicate, to a certain extent, the period of time, or duration, as well as the activity of the inflammation, and, under certain circumstances, its location and sequels. That form of chronic inflammation in which the process extends over a long period of time and is associated with the formation of fibrous tissue in excess is sometimes referred to as **productive inflammation.** The changes that take place in the interstitial tissue of the kidney in chronic interstitial nephritis may be taken as a type of this form of inflammation.[1] The view that all tissue changes associated with an increase in fibrous tissue are to be regarded essentially as manifestations of productive inflam-

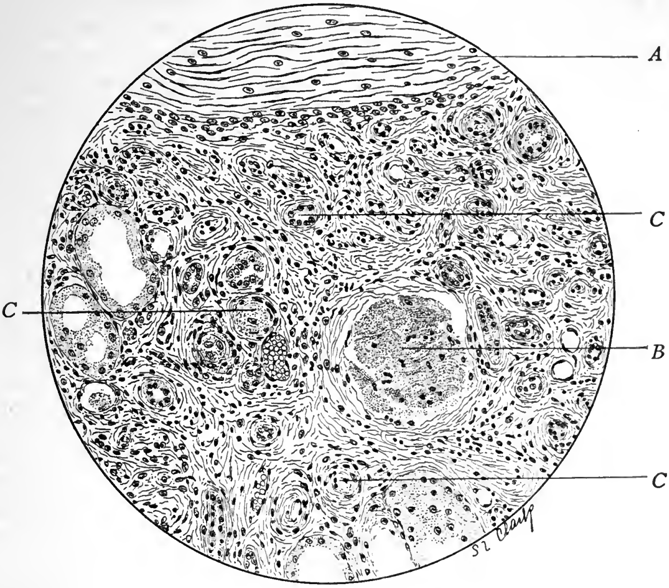


FIG 158.—KIDNEY, CHRONIC INTERSTITIAL NEPHRITIS.

A. Part of capsule. *B*. Malpighian body, showing advancing granular and fibrous changes with marked thickening of the capsule. *C*, *C*, *C*. Tubules in the midst of the newly formed connective tissue; the epithelium is wasted or absent and the tubular wall notably thickened. The larger tubes on the left and below are somewhat dilated.

mation is no longer strongly urged. Thus, in degenerations that involve parts of the glandular viscera the disappearance of the essential normal elements may be followed by the development of fibrous tissue. This is sometimes spoken of as "substitutive fibrosis," and by some is not considered to be an evidence of past or existing inflammation. Such increase in fibrous tissue is also called "noninflammatory hyperplasia," thereby differentiating it from the increase in fibrous tissue that is clearly consecutive to inflammation and constitutes the terminal tissue changes in many inflammatory processes. When considering the path-

[1] See Chronic Interstitial Nephritis, chapter on Diseases of the Urinary Organs, Part III

ology of organs, further reference will be made to chronic inflammatory processes and substitutive fibroses.[1]

Inflammatory processes not associated with infection are sometimes spoken of as simple or common. To speak of such processes as common in the sense that they are frequent is clearly an error, as most inflammations are due to infection. Inflammations due to some particular organism are called specific. While not restricted to syphilis, the term specific infection is most frequently applied to syphilitic lesions. When the essential secreting or actually functionating cells of an organ are involved, the inflammation is said to be *parenchymatous;* when the supporting tissue (connective tissue) is the principal seat of the lesion, the inflammation is called *interstitial.* By reason of the intimate physiologic and structural relation of the connective tissues of organs with the essential functionating cells it does not seem probable that an inflammation can ever be strictly parenchymatous or strictly interstitial. That one or the other tissue may be apparently more involved justifies, to a certain extent, this nomenclature. Suppurative, pyogenic, purulent, or phlegmonous inflammations have already been considered. Such inflammations are appropriately called *septic,* in contradistinction to the infrequent inflammatory conditions in which bacteria have no part—*aseptic inflammations.* When considering inflammations of the mucous membranes, reference will be made to catarrhal, pseudomembranous, fibrinous, croupous, diphtheric, gangrenous, suppurative, and hemorrhagic inflammations of those structures.[2] Dry, moist, serous, serofibrinous, fibrinous, plastic, adhesive, exudative, and other inflammatory processes affecting serous membranes will be considered with diseases of those structures.[3]

It will not be amiss, at this point, briefly to discuss the cardinal symptoms of inflammation and to indicate the relation that exists between these usually recognizable changes and the morbid processes to which they owe their presence. The more or less active inflammatory conditions, and even certain inflammations characterized by sluggishness, possess one or more of the so-called cardinal symptoms: namely, heat, pain, discoloration, swelling, and disordered function.

Morbid Physiology of Inflammation.—*1. Heat.*—Practically, the recognizable rise of temperature is dependent upon the increased amount of blood distributed in the area, which, coming from internal organs, possesses a temperature higher than the blood present in the superficial circulation under normal conditions. Theoretically, the following features are also active; it is not probable, however, that their influence is of practical import: (*a*) the increased cellular metamorphosis; (*b*) the increased oxidation that is going on in the area involved; (*c*) the friction of the increased blood-current and the impact of stasis may also increase the temperature.

2. Pain is due to pressure or to stretching of the nerves by the swelling, and to the irritant action of the inflammatory exudates upon the nerve filaments. At this point it is well to note that pain may be beneficent in inflammation, in that it secures rest of the part, thereby leading the patient to favor the progress of reparative processes.

[1] See Interstitial Pneumonia and Cirrhosis of the Liver, Part III.
[2] See Diseases of the Mucous Membranes, Part III.
[3] See Diseases of Serous Membranes, Part III.

3. Discoloration is dependent upon (*a*) the increased amount of blood in the area; (*b*) the proliferation of the cellular elements; and (*c*) the character of the inflammatory exudate; thus, the increased amount of blood may give rise to redness, which becomes scarlet, brownish, or bluish, passing through the different shades to black; the color depends on the vascularity of the part and the degree of stasis. In nonvascular exudates the structure may be white instead of red; this is shown in the cornea, in which the "ground-glass appearance" is observed; this gray, lusterless, cellular accumulation and granular change in the corneal corpuscles, as the cornea is avascular, cause no redness. Redness, when present, is represented by the injection of the adjacent conjunctiva. The exudate in inflammations of serous membranes renders the surface white, unless the inflammatory processes be hemorrhagic.

4. Swelling is due to (*a*) the increased amount of blood in the part; (*b*) the notable accumulation of leukocytes and, to a much less degree, the proliferation of cells; (*c*) undoubtedly the most important factor is the exudate in the perivascular tissue. As already stated when considering the development of the exudate, swelling may manifest beneficial tendencies. Under certain circumstances it becomes dangerous; thus, if the swelling be great, the capillary circulation may be obstructed and, as a result of faulty nutrition and of the activity of the inflammatory process, degenerative changes, necrosis, and even gangrene may occur. This unfortunate termination is sometimes observed in inflammation of the subcutaneous tissues (cellulitis, angioleucitis), where the extensive swelling cuts off nutrition to the overlying structures and gangrene ensues. Inflammation of the juxta-epiphyseal disc may lead to thrombosis of the capillaries supplying the epiphysis, followed by necrosis of that structure. It is not necessary to multiply examples, although reference should be made to the corneal sloughing that takes place as a result of intense swelling of the surrounding conjunctiva, cutting off ingress and egress of lymph from the avascular, transparent membrane.

5. Disordered function is due to (*a*) alteration in the tissue cells present, both the essential functionating cells and the interstitial elements; (*b*) the mechanical interference with function resulting from the exudates; and (*c*) the fact that the exudates impede the activity of the innervation upon which the function of all tissue so largely depends.

Systemic Phenomena of Inflammation.—These are largely embraced in the term *fever*, and are due to the absorption of bacterial toxins and other poisons engendered by the perverted metabolism and necrosis in the affected tissue. The character of the fever and the severity of its manifestation are dependent upon the activity of the agents absorbed. In the simple aseptic fluids taken up by the lymphatics and blood-vessels, from an ordinary sterile wound, such as is typified in a broken bone, the manifestations are slight and temporary. When the toxic substances absorbed contain the products of bacterial life, marked alteration in the tissue elements elsewhere in the body may occur. Degenerative and necrotic lesions are produced in the viscera independent of the presence of bacteria. The disturbances of glandular activity are represented in the diminished secretions and excretions. The epithe-

lial surfaces show, under the influence of bacterial agents, a decided tendency to undergo degenerative processes; this is most marked the more severe the infection, so that in the gangrenous and specific inflammations—for example, those of diphtheria—coagulation necroses in the large glandular viscera are not uncommon. The nervous phenomena that accompany inflammation are probably due to the direct action on the nerve substance of the toxins under consideration, or to the influence of the poison upon the capillaries distributed in the nerve tissues, giving rise to inflammatory or degenerative processes in those structures. Exactly what causes the condition called fever will be discussed later.

REPAIR.[1]

Cell Reproduction.—As a part of the processes of repair (repair modified by infection, regeneration, inflammation so called, hyperplasia, certain forms of hypertrophy, etc.), prolification, proliferation, or reproduction of cells must be studied. There are two methods by which cells are reproduced: (1) *Direct division*, or *amitosis;* (2) *indirect division*, also known as *karyokinesis*, *karyomitosis*, and, quite commonly, a more convenient term, as *mitosis*.

1. **Amitotic Division.**—In this form of segmentation the cell elongates and develops a constriction that involves both the cell protoplasm and the nucleus. This constriction is followed by a separation of the two portions, the nucleus first dividing and passing to the two ends of the protoplasm, which gradually separates, giving rise to two cells; during the process there is no manifest systematic change in the chromatin of the nucleus, as is seen in the next form.

2. **Mitosis.**—As a rule, the cell divides only into two parts; this is not, however, constant, as occasionally three cells may be developed simultaneously from one cell (J. Arnold). The steps of mitosis may be approximately stated as follows: In the resting nucleus the chromatin increases and groups itself as a skein, which later becomes thinner (*mother skein*). During this process the nuclear membrane disappears, and, if the cell possessed a nucleolus, this is lost sight of. Immediately following this—probably in progress at the same time—there are developed, apparently from the achromatin, delicate lines that pass off toward the two poles of the cell, giving the central portion of the cell an arrangement shaped like a spindle, and hence the name *nuclear spindle*. The chromatin now divides transversely to this nuclear spindle, and passes, one half in each direction, toward the points of the spindle. The mass of the chromatin at each end of what was the spindle now constitutes what are spoken of as the *daughter stars*. During the arrange-

[1] Maximow, "Experimentelle Untersuchungen über die entzündliche Neubildungen von Bindegewebe"; Funfter's Sup. "Ziegler's Beitrage," Jena, 1902. Pezzolini, "Gazz. Osp. e Clin.," 1901, No. 151. Minervini, "Virch. Arch.," 1904, Bd. 175, Heft 2, p. 238. Jurgelunas, "Ziegler's Beitr.," 1901, Bd. xxix, Heft 1. Mallory, "Jour. Med. Research," Dec., 1903, p. 334. Capaldi, Memor. Chirurg. Palermo, 25th year. Hektoen, "Jour. Med. Research," March, 1902, n. s., vol. ii. Schiffmann, "Centralbl. f. allg. Path.," 1903. Schleifstein, "Virch. Arch.," March 1, 1904, Bd. 175, Heft 3, p. 534. Taddei, "Atti Accad. di Sci. med. e nat. in Ferara," 1903. Loeb, "Jour. Med. Research," 1902, vol. viii, p. 109. Matsokua, "Virch. Arch.," Jan. 2, 1904, vol. 175, p. 32.

ment of the chromatin as daughter stars an hour-glass-like contraction of the protoplasm of the cell appears, formed by an annular narrowing gradually developed around the center of the cell. At first the daughter stars situated in the two poles of the cell are joined by delicate striation, which probably represents the remains of the achromatin formerly constituting the nuclear spindle; these lines disappear, the two masses of chromatin show no connection, and the hour-glass contraction is completed, separating the cell into two parts, each of which contains a daughter skein, which now rearranges itself as a resting nucleus, around which a new nuclear membrane may appear.

Lavdowsky has described another form of cell division that he calls *division by force*. It appears in this form: two portions of the protoplasm of the cell move in opposite directions, apparently pulling them-

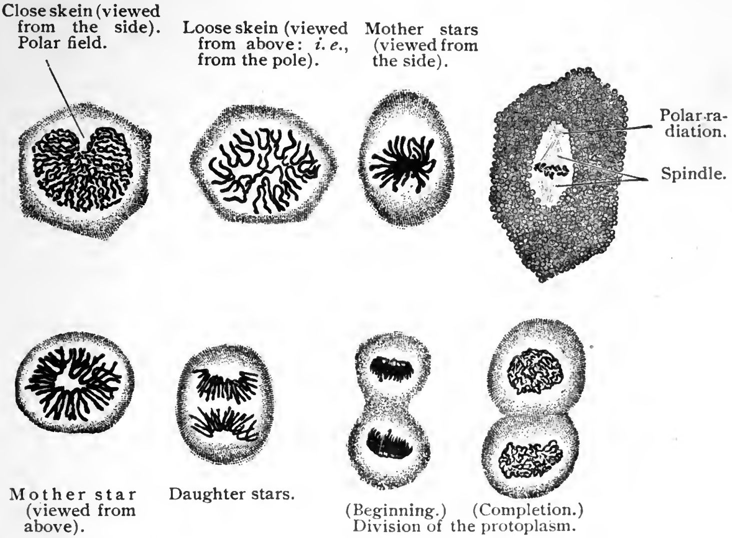


FIG. 159.—KARYOKINETIC FIGURES OBSERVED IN THE EPITHELIUM OF THE MOUTH CAVITY OF A SALAMANDER.—(*Stöhr.*) × 560 diameters.

The picture in the upper right-hand corner is from a section through a dividing egg of siredon pisciformis. The centrosomata, also the first stages of the development of the spindle can not be seen by this magnification.

selves apart. Thoma has described and illustrated this process as occurring in the white blood-cells of the frog when stimulated by electricity.

Inflammation is repair plus the removal of dead tissue or infection. When there is no dead tissue to remove, or when this is in a minimum, and when there is no infection, injury to tissue is followed immediately by the process of repair.

As studied by the surgeon, healing is said to take place in the following ways:

1. **Union by First Intention.**—Thus, if the surfaces of a recent wound be brought immediately in contact and retained, the following phenomena occur: Liquor sanguinis containing a variable number of red cells fills the interstices of the wound and extends laterally into the lymph-

spaces of the wound margins. Coagulation is facilitated by the presence of thrombin or its antecedents formed in the extravascular tissues. The resulting coagulated liquor sanguinis—so-called inflammatory lymph or fibrinous cement—affords a temporary binding between the two margins of the wound, affording sufficient solidity to permit the further progress of repair. The first step necessary is the removal of the dead cells and other structures which constitute irritating foreign bodies; this is accomplished by the leukocytes which migrate from the adjacent lymph-spaces and vessels. In the absence of infection the number of polymorphonuclear leukocytes is small, while the mononuclear are more numerous; proliferative changes and accumulating mononuclears give rise to a tissue made up of round or irregular cells to which, on account of their polymorphism, Maximow gives the name **polyblasts.** Many of these are indistinguishable from the lymphoid cells and large hyaline leukocytes, from which it is probable they are all derived; they are identical with the *small round cell* or *indifferent cell* of the older writers. Among these soon appears a cell apparently having an entirely different destiny. In its younger forms it may resemble the polyblast, but soon becomes fusiform and eventually develops into long spindles, from the tapering ends of which delicate fibrils can be seen extending a considerable distance from the body of the cell; this structure is called the **fibroblast.** Apparently it is the product of proliferative changes in the fixed connective-tissue cells of the part. The relation of the newly formed fibrous tissue to these cells renders it clear that the fibrils are in some way developed from them, but exactly how the elaboration of fibrils is accomplished is less certain. Of the many methods that have been suggested, three are deserving of consideration: (1) The older view that the fibrils resulted from elongation and attenuation of the cell protoplasm followed by disappearance of the nucleus is not in accord with the best information as to the method by which cells ordinarily accomplish the specific purposes toward which their activity is directed. (2) According to this view, the fibrils are formed at the periphery of the cell from which they are shaled off or shed, new fibrils arising as rapidly as the older become an integral part of the developing cicatrix. Eventually when the fibrous tissue formation is complete the nuclei of

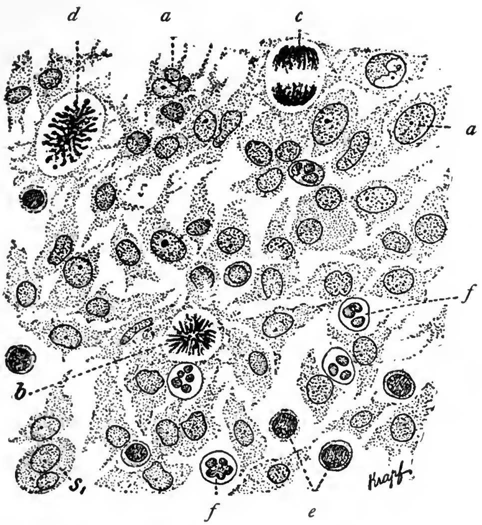


FIG. 160.—CELLULAR ELEMENTS OF FORMATIVE TISSUE.—(*Schmaus.*) × 500 diameters.

a, a. Polyblasts. *b.* Mother star. *c.* Daughter star. *d.* Skein stage. *e* Round or lymphoid cells. *f, f.* Polymorphonuclear leukocytes.

many of the fibroblasts disappear, others remaining as the fixed connective-tissue cells of the scar. (3) It is known that the matrix of bone and cartilage is formed through the secretory activity of cells (osteoblasts or chondroblasts) and that most other cells accomplish function by a process called secretion. In order to coordinate fibrogenesis with osteogenesis and chondrogenesis it is necessary to assume that the fibroblasts in a way secrete the fibrils forming the cicatrix; in other words, that the cicatricial tissue is laid down by these cells exactly as the matrix of bone or of cartilage is formed. It is possible to see in some of the fibroblasts a periphery of fine granules which by intracellular or extracellular coalescence might readily form the fibrils, and it is probable that this or some similar method is ordinarily followed in their production. The view that the fibrils are shed from the margin of the cell is in accord with their possible secretion, or at least is not inconsistent with that origin.

In addition to the cellular elements already mentioned as present in tissues undergoing repair there are a number of cells the nature and function of which are not accurately determined. Among these may be mentioned the plasma cell and the giant cells of repair. The **plasma cell** is about the size of the lymphoid or hyaline leukocyte, it possesses a round or oval nucleus and a structureless protoplasm which stains with varying degrees of intensity when exposed to the action of basic anilin dyes (is basophilic). While frequently present in reparative processes it has been shown by Councilman and others that this cell constitutes an important element in the interstitial exudate of acute, non-suppurative, interstitial nephritis, and in parenchymatous inflammations of toxic origin and associated with cell exudation. It is probable that the plasma cell is a derivative of a hemal leukocyte, possibly the lymphocyte, although upon this point additional data are needed. The function and fate of the cells are also undetermined. Another conspicuous cell in reparative processes is a large, round, oval or polymorphous body, varying in size from 10 μ to 40 μ or 50 μ and containing a number of nuclei; this is the **giant cell of repair.** Such elements are more common in tissues containing foreign bodies, but are not proportionate to the size or number of extraneous substances. The nuclei are less commonly peripheral than in the giant cell of tuberculosis, and the protoplasm is usually less intensely acidophilic, although neither of these differences is constant. The origin, mode of formation, and function of giant-cells have been the source of much controversy since their description by Johannes Müller in 1838. They probably arise in one of two ways: (1) Nuclear division without associated protoplasmic segmentation; (2) confluence of the protoplasm of cells, resulting in the formation of a type of giant cell resembling that caused by the massing of other cells, called plasmodia. It is probable that the second is the more common method by which these cells are produced. The number of nuclei present in the giant cell varies; as many as eighty have been observed in a single cell. The researches of Heidenhain, Koch, Metchnikoff, Soudakewitsch, Faber, Hektoen, and others, fully establish the inclusion and phagocytic power of giant cells.

The foregoing description of the cytology of reparative tissue has necessarily led past changes in other structures, notably the blood-vessels. During the early avascular stage the structure composed of

leukocytes and polyblasts, and possibly cells ancestral to the fibroblast, has been called *indifferent tissue*, *embryonic tissue*, or, including the later stages, *productive* or *reparative tissue*. The name embryonic tissue is based on the supposition that constituent cells possess capacities for growth comparable to some of the cells seen in the earlier stages of the developing embryo, and are competent to produce more than one kind of tissue, for example, fibrous tissue, bone, etc. It is probable, however, that the tissue eventually produced is dependent upon the origin of the formative cell; when these structures arise from connective tissue, an ordinary cicatrix is formed; when they are the progeny of bone cells, they give rise to bone, and though in both instances the morphology and stain reactions render them indis-

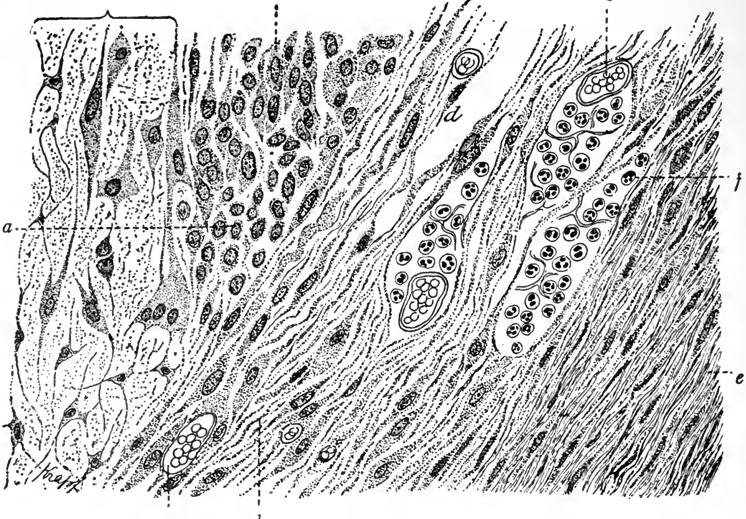


Fig. 161.—Granulation Tissue. Later Stage in Organization than Figure 160.—(*Schmaus.*) × 250 diameters.

a. Round or lymphoid cells. *b*. Fibroblasts. *c*. Spider cells, multipolar cells. *d*. Space from which cellular elements have dropped out; possible primitive lymph-spaces. *e*. Point where the evolution of fibrous connective tissue is most advanced. *f*. Leukocytes with several nuclei. Through this area will be seen young capillaries, branched and budding; the same are shown below the blood-vessel indicated by the upper *g*. *g*, *g*. Blood-vessels. *h*. Matrix of intercellular substance forming fibrillated tissue.

tinguishable, the tendency to elaborate structures identical with the mother tissue indicates potential differences.

In order to maintain the nutrition of the developing tissue vascularization is necessary. While in the embryo other forms of capillary development are recognized, the only form admittedly present in reparative processes is development by budding. From the walls of the nearest capillaries proliferating endothelial cells give rise to conic projections which extend into the developing tissue. These projecting buds, after passing some distance from their point of origin, unite with other buds, thus forming capillary loops, through which the circulation is established. The tissue previously known as embryonic tissue is now *granulation tissue*. When seen, for example, in the floor of an

ulcer, each loop or group of loops forms a minute elevation called a granule; hence the name granulation tissue. It is possible that capillaries formed in this way may later develop thicker walls, and may ultimately become arteries or veins. Around the newly formed capillaries the development of fibrous tissue continues. At first the cicatrix is red, or at least pinkish, the heightened color being due to the richness of its blood-supply. Later, contraction of the interlacing fibrous tissue occurs, diminishing, by pressure, the number and carrying capacity of the newly formed vessels, the tissue eventually becoming white. The tendency of developing fibrous tissue to contract gives rise to structural and functional disturbances in organs whose nutrition it so profoundly influences. The evidence of such contraction is clear in diseases of certain viscera, such as the liver in chronic interstitial hepatitis, and the kidney in chronic interstitial nephritis.

There is sometimes described a form of repair that closely resembles union by first intention—repair upon a *framework* or *scaffold*. To illustrate how this may occur, let us suppose that there is a large "dead space," such as would result from chiseling a cavity in bone; into this dead space blood oozes and coagulates. The fibrin forms a scaffold, upon which young blood-vessels and embryonic and granulation tissue advance from the sides and eventually complete the process of repair. Materials other than blood have been used for the scaffold; sponge, chips of bone, cartilage, ivory fragments, and allied substances that can be readily antisepticized are sometimes used.

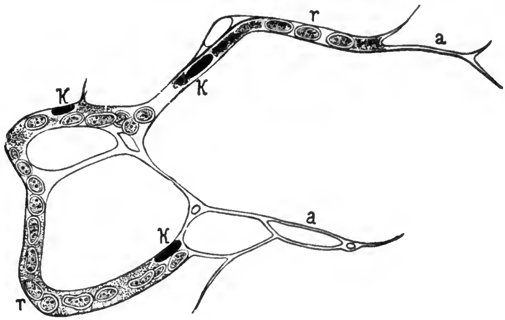


FIG. 162.

The formation of capillaries in embryonic tissue. *K, K, K*. Endothelial plates with protoplasmic projections, *a, a*, which later become capillaries. Other communicating branches are shown. A part of the vascular loop contains red blood-cells, *r, r*.—(*Landois*.)

2. Healing by second intention is said to occur in wounds the edges of which can not be brought together, and in which the scaffolding process, already referred to, is not available. The ordinary recent traumatic ulcer is an illustration of this process. Suppose that considerable skin surface is removed, and that a raw surface is presented for healing: Within a few hours a layer of coagulated fibrin and partly inspissated serum appears upon the surface of the wound. Dead elements within the viable tissue are attacked by the phagocytes and are removed, and proliferation of the connective-tissue cells and accumulation of leukocytes proceed to the formation of embryonic or formative tissue. Young capillaries spring out from the adjacent vessels and convert the formative tissue into granulation tissue. By continuous proliferation of the cellular elements, with pushing up of the capillaries, the cavity is gradually filled, and when this new tissue reaches the surface, covering over by epithelium occurs.

The epithelial regeneration is secured through the activity of the

epithelial cells near the edge; these proliferate, and by extension from the periphery, in favorable cases, gradually cover the granulating surface. Epithelium may be ingrafted upon the formative tissue, and additional centers of epithelial regeneration may, in this way, be established.

Another form of healing that is truly repair by second intention is sometimes referred to as **healing by third intention.** This is illustrated when two granulating surfaces are brought together; the two adhere, blood-vessels pass from one to the other, and cicatrization occurs, exactly as already described. The final cicatrization and ob-

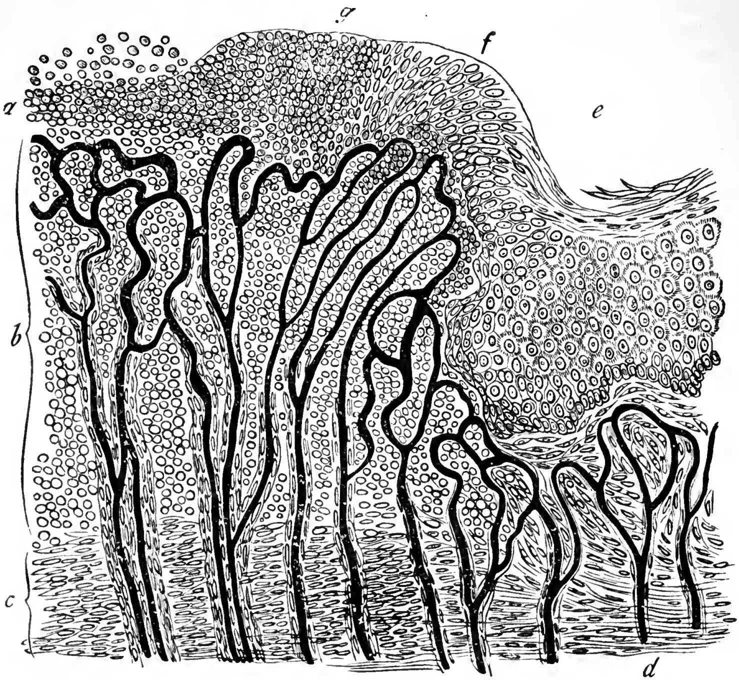


FIG. 163.—SECTION THROUGH THE BORDER OF A HEALING WOUND (Diagrammatic).—(*Rindfleisch*) × 300 diameters.

a. Surface of ulcer. *b*. Granulation tissue composed of embryonic tissue with the capillary loops developed from the vessels below. *c*. Later stage in the development of the granulation into spindle-cell elements; young cicatricial tissue that is older at *d*. *e*, *f* *g*. The epithelium spreading over the surface of the healing area.

literation of an abscess cavity is secured in this manner. After evacuation of the pus and destruction of the bacteria the collapsed walls, coming in contact, unite. It was once considered that union under a scab represented another form of healing, but it is now recognized that granulation and skinning over by epithelium, as already described, occur. It is not, therefore, a distinct process, but merely a form or combination of some of the foregoing.

A close examination of the forms of repair as just given will show a distinct resemblance of each to all the others; the difference, so striking clinically, is far less marked when we come to investigate the essential

changes through which each must pass. In all there is the same preparation for repair, usually effected through the activity of phagocytes. Following or accompanying this, proliferation of pre-existing elements leads to the development of fibroblasts, through the presence of which final cicatrization is brought about. Even the epithelial regeneration is not essentially anything out of the common, as wherever the skin has been wounded, whether the injury be microscopic or large, proliferation and extension from the margin must be the only normal method of covering the young connective tissue.

Regeneration.—Repair may occur without regeneration. Thus, muscle may be repaired by fibrous tissue, the scar joining the severed ends of the muscle. It does not seem, however, that new muscle is produced, certainly not in quantities of material value in the restoration of destroyed areas. With regard to nerve and bone, this is different; repair terminates in regeneration, and new tissue may be produced that is identical with that previously present. Regeneration occurs in but few tissues; nerve and bone are the best examples. Repair seems possible in almost any tissue, but such repaired tissue may be, in part at least, functionally inactive, because regeneration has not been complete. Thus, a large cicatrix upon the skin does not contain sweat-glands or hair-follicles, and, while it protects the subcutaneous tissues, it performs none of the special functions of the skin. Destroyed kidney tissue may be followed by repair, but apparently not by regeneration.

Many authorities regard regeneration and repair as essentially identical processes; thus, when repair terminates in the formation of fibrous tissue, they say it is regeneration of the fibrous tissue. No one doubts the regeneration of fibrous tissue, but when a large area of the skin or a considerable volume of an organ is converted into fibrous tissue, with the total disappearance of every other structure but the fibrous tissue, it certainly is not correct to say that the organ is regenerated, and the enormous increase in fibrous tissue amounts to something more than the mere regeneration of that element. Repair, as described here, is synonymous with regeneration of the fibrous tissue described by other writers. Regeneration, as already defined, implies the production of new elements structurally and functionally allied to, if not identical with, the destroyed tissue that they replace. The regeneration of nerve and bone is considered with the special pathology of those structures.[1]

[1] See chapter on Nervous System and chapter on Diseases of Bones, Part III.

CHAPTER XII.

TUMORS.

The word *tumor*, which means *swelling*, has been variously applied in medical literature. Some writers evidently include among the tumors cellular collections clearly of inflammatory origin; to such aggregations of cells is given the name inflammatory tumors, granulation tumors, etc. The tendency at present is to exclude all such masses and restrict the term tumor to—(1) neoplasms; (2) cysts.

NEOPLASMS.[1]

A neoplasm is a morbid growth characterized by a tendency to persist or increase in size, independently of changes in the metabolism of contiguous or systemic structures, and performing no useful function. In the present state of our knowledge the most striking phenomenon in connection with tumors is their apparent purposeless existence; the inflammatory new growths result from the reaction of the tissues to an evident cause, and are characterized by efforts to overcome the inciting agent or protect contiguous tissues, or the system at large, from further injury. The inflammations and infections with which we are familiar are attended by distinguishing clinical phenomena and more or less characteristic anatomic changes. The increased tissue growth seen in hypertrophy supplies structure for augmented function upon which its evolution largely depends and with the disappearance of which the hypertrophy tends to subside.

The general tendency to regard tumors as without function is correct in part only; Waring[2] states that renin and pepsin may be extracted from the cells in gastric cancer, and that from both the primary and secondary growths originating in the pancreas, ferments normally developing in that gland may be found in varying quantities. In carcinoma arising from epithelium of the thyroid, symptoms of hyperthyroidism may be present, disappearing when the tumor is removed and reappearing with recurrence even when the latter is metastatic. Albrecht[3] describes an endothelioma the histology of which indicated that red blood-cells were being produced within the tumor.

General Considerations.—For purposes of clinical description and pathologic study certain terms are used in connection with tumors with which the student should be familiar. In studying tumors for either diagnostic or pathologic purposes there should always be a definite

[1] For clinical study of tumors the works of Bland-Sutton, and Senn are especially recommended. An exhaustive clinical and pathologic review of tumors is given by Borst, "Die Lehre v. d. Geschwulst. m. e. mikroscop. Atlas," Wiesbaden, 1902. See also Chantemesse and Podwyssotsky, "Les Processus Généraux," 1905, vol. ii, p. 61.

[2] "Jour. of Anatomy and Physiology," London, vol. xxviii, p. 140.

[3] "Münch. med. Woch.," July 8, 1902.

routine in the method of examination, as has already been insisted upon when considering postmortems. The following order is commended: (1) Describe the tumor; (2) its relation to surrounding tissue and organs; (3) the history of the tumor; (4) the history of the patient. In purely clinical studies it is common to begin with the history of the patient, and the foregoing order may be reversed without affecting its usefulness.

1. In describing the tumor the following points may be of aid in diagnosis, and ought to be developed in the history: (*a*) Its *situation*, superficial or deep, on, or in contact with, epithelial surfaces, deep in a purely connective-tissue area, or within a structure composed of one or both tissues; this includes the organ involved. (*b*) The *conformation* of the tumor: Is it globular, flat, bossed, pendulous, pedunculated, pyriform, conic, excrescent, polypoid, dendritic, sessile, cauliflower, tuberous, lobulated, fungoid, etc.? (*c*) The *size* of a tumor may be approximately estimated before it is removed from the body. After removal accurate measurements should be made and the mass should be weighed. (*d*) *Number:* Is the tumor single—that is, solitary—or is it multiple? If multiple, was it so from the beginning, or was one tumor followed by a succession of others? Are all the tumors apparently alike, having the same conformation, consistency, and similar location? (*e*) *Consistence:* Some tumors are so soft that they fluctuate; others are *semisolid*, *gelatinoid*, *solid*, *hard*, or even *eburnated*. (*f*) *Color:* This includes the color of the overlying structures. The tissue covering a tumor may be normal or inflamed; it may contain tortuous veins; it may be edematous, or even pigmented; it may be so vascular that the color is of a blood tint, either pink or red, or, in some instances, cyanotic. (*g*) The *mobility* of the tumor: Is the tumor movable in the tissue that surrounds it? Is it movable only with the organ involved, or has the tumor, as well as the affected organ, become attached to adjacent structures? (*h*) *Sensibility:* Is the tumor painful, tender, sensitive to changes in temperature or to atmospheric conditions? Is the pain or tenderness constant, remittent, or intermittent?

2. The *influence of the tumor, if any, upon surrounding structures:* Are they involved, inflamed, edematous, sensitive, or anesthetic?

3. The *history of the growth:* How long has the tumor persisted? Is it growing rapidly or slowly? Has its growth been constant or intermittent? Is its growth influenced by any of the functions of the body? (For example, some tumors in women enlarge during menstruation.) What *pathologic processes*, if any, are present within the tumor? Is there evidence of inflammation, gangrene, cyst formation, suppuration, infiltration, or of degeneration?

4. *History of the patient.—Age:* Some tumors appear in the young, others are more frequent in middle life, and some occur in the old. *Sex:* Some tumors are more frequent in the male; others, in the female. Carcinoma of the male breast occurs in about one per cent. of all cases of mammary cancer. *Social condition.* Married or single. *Occupation:* Certain tumors have long been recognized as frequently associated with given occupations: *e. g.*, chimney-sweep's cancer. *Habits:* A few tumors are dependent, apparently,—to a certain extent, at least,—upon given habits: *e. g.*, smokers' cancer. *Heredity:* There is reason to believe that in some tumors inheritance may play a part. Has the *general*

nutrition of the patient been influenced in any way, and is the influence purely mechanical. such as may result from the weight of the tumor, or is it attributable to the position? Have ulceration or infectious processes modified general nutrition? In the absence of any other explanation, it may be inferred that the tumor itself has been prejudicial to the patient's health.

Previous history of the organ or tissue involved: Is there a history of injury or inflammation, such as might occur in the breast during lactation? Has there been any *previous disease of the gland or structure involved?*

Causes.[1]—It is not improbable that different tumors arise as a result of the action of various causes. As, however, we know very little concerning the exact etiology of any particular tumor, certain general considerations are permissible. The older theories, attributing the occurrence of tumors to alterations in the humors of the body, particularly of the blood, and similar hypotheses, may at once be discarded. The following hypotheses are deserving of consideration:

1. The Durante-Cohnheim Inclusion Theory.[2]—This theory is based upon the supposition that, during embryonic development and the specialization of the cells entering into the formation of organs and adult tissues, more embryonic elements are produced than are necessary, and that these cellular elements become quiescent in the tissues, where they may remain, constituting embryonic "rests" or "remnants," from

[1] The scope of this work does not permit the introduction of exhaustive references. Those interested in the literature bearing on the etiology of tumors may find or can trace the most important communications from the references which follow. I have purposely divided them into two groups. Articles supporting the parasitic origin of neoplasms: Bosc, "La Presse Méd.," Jan. 14, 1903, p. 53. Schüller, "Parasitäre Krebsforschung und der Nachweis der Krebsparasiten am Lebenden." Abhandlungen aus dem Gebeiten der Krebsforschung und verwandten Gebieten, 1903, Heft 1, Berlin; also "Centralbl f. Bakt.," Dec. 12, 1904, p. 547. Hornus, Thesè de Paris, 1905. Sanfelice, "Riform med.," Sept. 6, 1904; also "Wien. med. Presse," 1904, No. 42. Plimmer, "Jour. Path. and Bact.," 1894, vol. ii, p. 486. Podwyssotsky, "Zeit. f. klin. Med.," vol. 47, Nos. 3 and 4. Feinberg, "Wien. klin. Woch.," 1903, Nov. 5, p. 1236, and Nov. 12, p. 1272. Gaylord (and others), Fourth Ann. Report, Cancer Lab. of the N. Y. State Board of Health, 1902–03. Robertson and Wade, "Lancet," Jan. 28, 1905. Monsarrat, "The Hospital," Jan. 30, 1904. Roger and Weil, "Arch. de Med. Exp. et Anat. Path.," March, 1904, p. 145. Leyden, "Deut. med. Woch.," May 8, 1902.

Articles attributing neoplasms to causes other than parasites: Farmer, Moore and Walker, "Royal Soc.," Dec. 10, 1903. Foulerton, "The Practitioner," July and August, 1902. Futterer, "Medicine," March, 1902. Senn, "Med. Record," July 13, 1901. Lubarsch, "Patholog. Anat. u. Krebsforschung," 1902. Rogers, "Annals of Surgery," Aug., 1903, p. 280. Bashford and Murray, "Lancet," Feb. 13, 1904, p. 413. Honda, "Virchow's Arch.," clxxiv, Oct., 1903, p. 96. Hewlett, "Jour. of State Medicine," Nov., 1904. Morris, "Lancet," Dec. 12, 1903, p. 1634. Hertwig, Festschrift zur von Geburtstage von E. Hæckel, 1904, p. 303. Richardson, "N. Y. Med. Jour.," Aug. 27, 1905, p. 389, very full bibliography. Cohn, "Zeit. f. klin. Med.," vol. 56, Nos. 1 and 2. Beard, "Lancet," Feb. 11, 1905, p. 385. Orth, "Ann. of Surg.," 1904, xi, No. 6, p. 733. Greenough, "Jour. of Med. Research," Jan., 1905, p. 137. Nichols, "Jour. of Med. Research," Jan., 1905, p. 187. Adami, "The Medical Chronicle," June, 1900, also "Yale Med. Jour.," March, 1901. Baldwin, "The Physician and Surgeon," Feb., 1903, p. 49. Grünbaum, "Brit. Med. Jour.," Dec. 17, 1904, p. 1634. Israel, "Arch. f. klin. Chir.," 1902, vol. 67, No. 3.

[2] Monti ("Fundamental Data of Modern Pathology," Sydenham Translation, p. 51) has shown that Durante enunciated this theory in all its essential details before the appearance of Cohnheim's publication.

which, later, tumor formation takes place. Barfurth showed that it was possible for experimentally displaced germinal layers to develop in a new condition, and Zahn, followed by Leopold, proved that fetal tissues, especially cartilage, withstood transplantation far better than fully developed structures. Roux demonstrated the structural existence of the hypothetic bodies from which Cohnheim thought tumors arose. Such embryonic rests or remnants would be exceedingly likely to occur where developmental processes are complex, as, for example, where different forms of epithelium join. Such points of tumor election undoubtedly occur, as is shown by the development of cancer at the various orifices of the body and at points of epithelial transition, such as the lip, cervix uteri, etc. This theory also explains to advantage the occurrence of chondroid tumors in or from bone, and of melanotic sarcomata from quiescent pigmented cells in moles, and affords a most acceptable explanation for the development of dermoid cysts. The theory, however, is wanting in several ways. In the first place, admitting the occurrence of these remnants, it would appear that a further etiologic factor is necessary in order to stimulate them to renewed activity. Another objection is afforded by the fact that many localities in which complex developmental processes occur, such as the heart and the nervous system, are singularly free from tumors, and that when they do occur in such tissues, they are not commonly situated at points at which the complexity of development is most marked. Epithelial rests are sometimes demonstrable, and yet no tumor formation occurs. The occurrence of tumors as the result of trauma (to be considered later) is inconsistent with this theory.

2. *Injury and inflammation* appear to be, in a certain percentage of tumors, important etiologic factors. Persistent or long-continued irritation seems to favor the development of tumors belonging to the epithelial group. As examples of such tumors the following may be mentioned: Carcinoma of the scrotum in chimney-sweeps; epithelioma of the arm in workers with paraffin and tar; smokers' cancer of the lip or tongue and cancer of the tongue apparently due to injury by a carious tooth; and epithelioma orginating in the margins of chronic ulcerative processes. Among the nonmalignant epithelial tumors the development of which appears to be favored by injury or irritation may be cited the papillomatous masses due to the accumulations of irritating discharges particularly around the anus and external genital organs, when the parts are not kept properly cleansed. Sarcoma following fracture or injury of bone, and fibroneuromata of the severed ends of nerves after amputation, may be mentioned as connective-tissue tumors offering strong support to this theory. The occurrence of tumors at points particularly liable to injury is another argument in its favor.

Numerous objections have been made to the acceptance of this theory. In about eighty-five per cent. of all tumors no history of injury can be obtained. On the other hand, the frequency with which injuries are received is not at all in proportion to the total number of tumors occurring. Parts particularly subject to injury, such as the hands and feet, are not commonly affected, and the nipple, which is frequently injured, is rarely the seat of a tumor.

3. *Parasitic Influence.*—The germ theory has been invoked to explain the formation of tumors, particularly the malignant neoplasms, in

which metastases are conspicuous. By some the essential parasitic body is believed to be an animal parasite belonging to the protozoa and resembling, if not identical with, the coccidia already described. (See p. 184.) Others believe that the infecting body is a vegetable organism belonging to the blastomycetes. In further support of the parasitic origin of tumors the demonstrable autoinoculability of cancer is adduced.[1] Thus, it has been shown that cancer of one labium may attack the point of contact upon the opposite labium; cancer of the cervix may attack the contiguous vaginal vault; and cancer reaching the peritoneal surface may show a similar inoculability. It may be said at this point that such inoculability may be an evidence of grafting, just as epithelial cells may be grafted from place to place, or from one individual to another—skin grafting—without of necessity invoking the intervention of any parasite. A similar explanation is offered with regard to the grafting of cancer from one animal to another. The inoculation of tumors thought to be sarcomata, and occurring on the genitalia of dogs, is believed by some to be an evidence of the inoculability of sarcomata. Others maintain that the tumor in question is not a sarcoma, but that it belongs to that group of inflammatory embryonic cellular collections not easily differentiated from round-cell sarcoma.

4. *Parasitism of Cells.*—It is not impossible that normal cellular elements may take on a certain parasite-like property that, in the presence of reduced resistance afforded by other elements, permits of their extension beyond normal limits. Thus, in cancer cellular elements that we believe to be of epithelial origin are found abundantly infiltrating connective tissues Normally, epithelium does not so extend, nor, in most instances, even when introduced experimentally, does it acquire any such property. Should further experiment show that conditions may arise under which epithelium can acquire or manifest the faculty of intraconnective-tissue growth, without the intervention of any other factor, we may assume that the manifestation of this parasite-like character leads to the development of cancer.

5. Adami presents a most fascinating argument in favor of his view that whatever may be the origin of tumors, the most important element in their production is the fact that the cells forming the neoplasm give up the habit of function and acquire the *habit of growth.* Reproduction is of course an essential function in all cells, but in addition to proliferative power every cell is endowed with the inherent capacity to perform some specific duty, in the consummation of which it utilizes more or less of the energy that it is able to transform from the nutrition supplied. If the cell ceases to perform this specific function, whatever that duty may be, the energy previously converted in that direction is now transferred to the reproductive capacity of the cells, thereby leading to proliferation in excess of the normal. The originator of this suggestive hypothesis fully recognizes the necessity for some reason accounting for the cell's acquisition of the habit of growth at the expense of the habit of function. The fact that malignant neoplasms of epithelial origin, and particularly those arising from the mammary gland and uterus, appear at a time when function is on the decline, is fully in sup-

[1] See Loeb, "Jour. of Med. Research," vol. viii, June, 1902, p. 44; "Virchow's Arch.," 1903, Bd. 172; "Amer. Med.," March 14, 1903, vol. v, p. 412. Dagonet and Auclaire, "Arch. de Méd. Exp.," Sept., 1904, p. 552.

port of Adami's view. He further maintains that irritation, parasitic or otherwise, may so modify the cell that proliferation becomes excessive and secretion or other specific function proportionately diminishes.

6. Predisposing Causes.—The foregoing brief consideration of the most plausible reasons advanced to explain neoplastic growths indicates our ignorance of the essential etiologic factor in tumor formation. There are, however, certain predisposing elements worthy of consideration. Some of the conditions previously considered may be active only in this way. Trauma and inflammation may predispose to tumor formation, just as they predispose to infection, and long-continued irritation or prolonged ulceration may act only as predisposing elements. With regard to age, it may be said, in a general way, that physiologic activity favors the development of sarcoma, while senescence, or physiologic decline, predisposes to the occurrence of cancer (Da Costa). The influence of inheritance can not be entirely ignored, although it is probably slight.

Neoplasms are subject to two general laws:

1. **Müller's Law.**—*The tissue that forms the tumor has its type in a tissue of the organism, either adult or embryonic.* By this is meant that, no matter what the cellular elements of a tumor may be, such elements occur as normal structures in the adult tissues or in the tissues of the embryo at some period of its development.

2. **Virchow's Law.**—*The cellular elements of a tumor are derived from the pre-existing cells of the organism.* Virchow adds that they are the progeny of the cells of the connective tissue—a view clearly incorrect with regard to many neoplasms.

By the acceptance of these two laws we arrive at the fact that tumors spring from structures once normal, and represent, when fully developed, tissues that were normal; in other words, tumors are not importations into our bodies, but, like all other morbid processes, are perversions of normal cellular activity.

Tumors, in a general way, obey the laws that regulate normal structures, yet to some extent they live independently of the surrounding tissue. They usually possess their own circulation, and disseminate and proliferate at the expense of the adjacent tissue. While the patient may show every evidence of failing nutrition, and the adult and fully formed tissues of the body are undergoing progressive wasting, the tumor cells may not lessen in the least the rapidity of their growth.

Tumors are said to enlarge or to extend either by (*a*) **interstitial growth** or by (*b*) **dissemination.** By the former is meant that the growth within the tumor is uniform; that it increases in size by proliferation of its cells, without any dislodgment except that incident to one cell pressing upon and altering the position of another during the process of multiplication. Such tumors are likely to form capsules, the **capsule** developing either as a part of the tumor or by condensation of the surrounding tissue. The simple nonmalignant tumors may have capsules formed in either of the two ways indicated, but the malignant neoplasms are less likely to have anything like a capsule, by reason of the fact that they grow largely by dissemination.

(*b*) **Growth by dissemination** is said to be—(1) **growth by infiltration;** (2) **growth by metastasis.**

1. **Local dissemination** or **infiltration** is an extension of the tumor

into the surrounding tissue; this usually occurs by the entrance of the tumor cells into the lymph-spaces. Tumors growing by infiltration possess no sharply defined border, and are, therefore, without capsules, thus rendering the surgeon unable to determine definitely how far from the neoplasm it is necessary to keep in order to remove all of the tumor tissue.

2. **Metastasis.**—When, as just indicated, the tumor cells penetrate the primitive lymph-spaces, it will be seen how easy it is for such infiltrated cells to be caught in the lymph-stream and carried to the lymph-nodes into which the lymphatics of the area involved empty; such extension is most common in cancers, although it may occur in sarcoma, and is known as **metastasis by the lymph-stream.**

Extension of neoplasms by the lymphatics should, and ordinarily does, include **metastasis by the lacteals.** The latter is of infrequent occurrence, but when present gives rise to appearances that may mislead the uninitiated. The lacteal vessels of the intestinal wall and mesentery become tortuous, cord-like, and irregularly enlarged, sometimes presenting a moniliform aspect. In some cases the condition is associated with a chylous transudate in the peritoneal cavity: often there is no such evidence of obstruction. Usually emaciation or other evidence of malnutrition is extreme and unaccounted for by the character or extent of the growth.

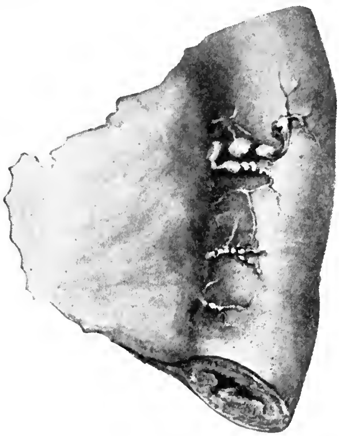


Fig. 164.—Small Intestine.
Dilatation of the lacteals due to sarcomatous implication of the receptaculum and adjacent tissues. The primary growth in this case was thought to have been in the adrenal. (Drawing ½ natural size.)

Tuffier[1] calls attention to cutaneous inoculation from ulcerating surface cancers. He believes that the small outlying nodules often adjacent to carcinoma of the breast are due to **transcutaneous autoinoculation.** I have seen a few instances of this type of neoplastic extension. It is well known that when an ulcerating malignant tumor is constantly in contact with a previously healthy surface the tissues of the latter may be invaded by the growth. In this way a neoplasm of the alveolar process may reach the mucosa of the cheek or tongue, a cancer of the cervix invade the vaginal vault or a malignant tumor of one labium inoculate the apposed surface of the vulva or thigh.

Metastasis by the Blood.—In certain tumors, particularly in sarcomata, the walls of the blood-vessels are poorly formed—indeed, nothing structurally comparable to the normal wall may be demonstrable; the blood traversing such tumors passes through what may be called sluiceways, the walls of which are not uncommonly formed entirely of tumor cells. These cells may drop off into the blood-stream and be carried along as emboli (neoplastic emboli), reproducing the tumor wherever they lodge. Again, a tumor may infiltrate the wall of the blood-vessel

[1] "La Bull. Méd.," Dec. 3, 1904.

and project into its interior, and small fragments, breaking off, may be carried to distant parts. The walls of the veins being thinner than those of the arteries, infiltration is rendered easier, and the circulatory conditions make the consequences more disastrous. Neoplastic emboli formed by penetration of the femoral artery can be carried only to the structures of that limb; if, however, the emboli be thrown into the femoral vein, their next point of lodgment would probably be the lung.

Pigmentation occurring in tumors may result from hemorrhage within the tumor and from the disintegration of blood coloring-matter, or it may be due to the fact that the neoplastic cells produce a pigment, such as is seen in the chloroma, melanotic sarcoma, and a few other tumors. It may also be due to the development of certain bacteria, particularly if the tumor be ulcerated.

Classification.—Clinically, tumors are said to be (*a*) **benign** or (*b*) **malignant.** By the former is meant that the tumor of itself does not necessarily involve danger to life, while the latter implies that, if undisturbed, the neoplasm will eventually prove fatal. A tumor ordinarily innocent or benign may destroy life simply by its location; for example, a fibrous tumor growing on the inside of the skull. This, however, does not justify our placing fibrous tumors with the malignant neoplasms, as the fact that it proves fatal, in the particular instance cited, is what Park has termed "malignancy by accident of location." In this connection it is well to recall that benignancy and malignancy are relative qualities, and that sometimes a neoplasm, possessing the clinical and pathologic attributes that are practically always accompanied by malignancy, may astonish the observer by rapidly disappearing. Cathcart[1] has collated numerous instances going to show that the usually sharply drawn line between innocent and malignant tumors is not always justified by clinic and pathologic data. Osler reported a number of cases of clearly established cancer in which, although recurrence followed operation, the tumor finally disappeared. This so-called spontaneous cure of malignant tumors is so infrequent that clinicians commonly ignore its occurrence. The conversion of non-malignant into malignant tumors is much more frequent; fibromata and myomata are sometimes transformed into sarcomas, and adenoma and papilloma into cancer.

At one time it was quite the custom for clinicians to classify tumors according to some symptom or peculiarity of shape. As examples of this may be mentioned, scirrhus, for hard, and encephaloid, for soft cancer; again, bleeding tumors, when fungoid, all came under the one head, "fungus hematodes." No fully satisfactory classification of tumors can be made at present; when we become familiar with their etiology, it is probable that more may be accomplished. The extension of our knowledge as to the minute structure of tumors has led to a classification based upon their morbid histology and histogenesis. Even if possessing no other advantages this basis offers a method by which neoplasms may be brought into related groups, thereby facilitating clinical and pathologic study.

Classification Based on Histogenesis.—Granting the correctness of the law of Müller, a tentative classification is possible, based upon the resemblance of tumors to the normal tissues, either adult or embryonic.

[1] "Brit. Med. Jour.," June 4, 1904, p. 1300.

All tissues spring from one of two types: (*1*) *Epithelium;* (*2*) *connective tissue.* Tracing these back to the blastodermic layers, they are developed as follows:

(*1*) *Epithelium*, from the epiblastic and hypoblastic layers (or outer and inner layers) of the blastoderm. (*2*) *Connective tissue*, from the mesoblast (or middle layer) of the blastoderm. All neoplasms spring from one of these two types, each type of tissue having two varieties:

(1) **Epithelium:** (*a*) *Adult* or *typical;* (*b*) *embryonic* or *atypical.* (2) **Connective tissue:** (*a*) *Adult* or *typical;* (*b*) *embryonic* or *atypical.*

Adult or *typical* tumors are those having their type in the adult body; clinically, these are *benign.*

Embryonic or *atypical* tumors are composed of cellular elements resembling those found in the embryo at some stage of its development; clinically, such tumors are *malignant.*

EPITHELIAL TUMORS.

Adult Epithelial Tumors.

I. Papilloma.—These growths are formed from cutaneous and mucous papillæ, and consist of a fibrous stroma, or stem, containing blood-vessels and lymphatics, and possessing an epithelial investment. The epithelium is of the kind normal in the particular situation in which the growth is located. The histologic structure of a papilloma resembles that of the ordinary papilla, and consists of a basis of connective tissue, richly cellular, from which project toward the surface numerous papillary processes, each process supporting blood-vessels that end in a capillary loop, the whole being enveloped in a covering of epithelium. Tumors of this class are commonly the product of chronic irritation, particularly when the latter is associated with a low-grade inflammatory process. Irritating discharges, especially from the genital and anal borders, may lead to the development of warts. A jagged tooth, by constantly subjecting the mucosa to injury, may give rise to papillomas of the tongue or cheek.

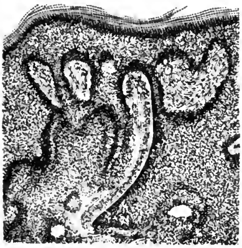


Fig. 165.—Papilloma.—(*Gould.*)

The papillæ vary in length: in the ordinary wart they are short; in the *villous papilloma* they appear as long, delicate fibrils, giving off secondary and tertiary shoots. On the skin the epithelial covering is thick, hard, and stratified, and actually binds the papillæ into a solid mass; on mucous membranes the slender vascular processes are covered with very delicate and easily lacerated epithelium.

Site.—Papilloma may appear anywhere on the skin or mucous membrane; as a rule, they grow from, and closely imitate, pre-existing papillæ. They rarely occur where no papillæ exist; in such rare cases the connective-tissue core springs directly from the subepithelial connective tissue—this is the case in the *stomach* and *larynx.*

Clinical Characters.—Clinically, warts are benign, or innocent. They may occur at any age; may be single or multiple; may disappear without any operative interference: this is especially true of multiple

warts. When occurring on mucous surfaces, they are highly vascular, and, owing to their thin epithelial covering and delicate connective-tissue matrix, are easily torn, sometimes giving rise to fatal hemorrhage. This is especially true of papilloma of the bladder and similar growths occurring in the urethral orifice. In the young, warts are occasionally transformed into sarcomata; in advanced life warts and warty surfaces (ichthyosis linguæ) may be converted into cancer.

Varieties.—(1) *Skin warts;* (2) *villous warts;* (3) *intracystic warts.*

1. Skin Warts.—(See Fig. 165.) Skin warts are overgrown papillæ, and on section the epithelium will be found to pass from one papilla to another in an unbroken line without invading the fibrous framework. They vary in size, and may become mottled with black pigment (melanotic). Cutaneous warts may be single or multiple, and may disappear in one area and appear in another, thus leading the laity to believe them migratory. Ordinarily, the cutaneous papilloma appears as a hard, abruptly elevated mass, apparently of epithelium, presenting an irregular or "warty" surface, usually divided by deep fissures. On section, the relation between the stroma and the epithelium may be seen even with the naked eye.

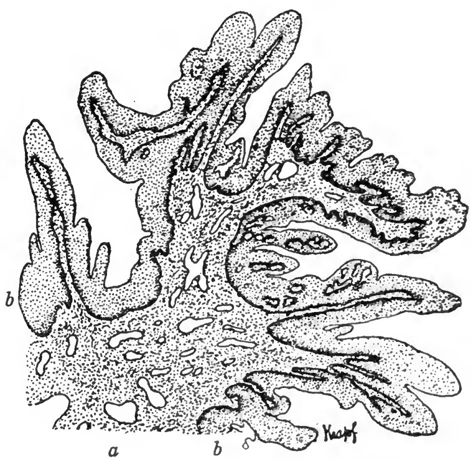


FIG. 166.—PAPILLOMA WITH TENDENCY TOWARD VILLOUS FORMATION.—(*Schmaus.*)

a. Connective-tissue basis containing numerous blood-vessels *b*, *b*. Epithelial covering.

2. Villous Warts.—These commonly spring from the mucous membrane, usually of the bladder, and occasionally of the renal pelvis; the condition is termed *villous disease*. The general appearance of the long, branching, feathery tufts resembles that of the delicate chorionic villi; structurally, the villi consist of a connective-tissue core traversed by delicate blood-vessels, the whole being surmounted by epithelium. They may be *single* or *multiple*, sessile or pedunculated. The detachment of small villi may occasion hemorrhage, which, with frequent recurrence, gives rise to profound anemia. The size of the villous mass often bears no relation to the severity of the hemorrhage; the writer has examined, at autopsy, a fatal case in which the papilloma was not larger than a grain of wheat. The detachment of villi is usually brought about by their being forced, during the last stage of urination, into the urethra, where fimbriæ are caught; distention of the bladder pulls upon the incarcerated projections, breaking them off, and thereby inducing hemorrhage. Carcinomatous transformation of vesical papilloma occurs.

3. Intracystic Warts.—These may occur within almost any cyst cavity lined by epithelium, more especially those cysts developing in glands: *e. g.*, mammary, thyroid, and ovarian cysts. In cysts formed

in the mammary gland, particularly in those cysts arising during the growth of fibrous tumors of the breast, the wall may be lined by a papillomatous outgrowth. Tumors composed of papillomatous masses in the interior of dilated galactophorous ducts or mammary acini are spoken of as *intracanalicular papillomata.* Sometimes the cyst is said to be papillomatous. In many instances it is quite impossible to determine whether the cyst preceded the papillary growth or whether the reverse was the case. Examination of a number of such cysts usually shows that the papilloma is evidently a secondary process. Occasionally, the cyst may be distended with the papillary masses, the fluid, probably present at some time, having entirely disappeared. Cysts containing such papillomatous masses are sometimes seen in the liver. The villous outgrowth resembles that of villous papilloma, and the epithelial covering is usually the same as that of the cyst wall; it may be cylindric, tall or flat, and even ciliated. The size of such masses varies within wide limits, and the fact that their presence is at times unsuspected would lead one to regard them as sources of no danger. Occasionally, however, scirrhus of the breast follows or is associated with this form of papillary disease.

II. Adenoma.—An adenoma is a tumor constructed upon the type of a gland. Adenomata are of slow growth, and are believed to have their origin in some quiescent, congenitally displaced rudiment; their ducts do not communicate with the normal gland nor do their acini elaborate a secretion; they are, as a rule, completely encapsulated, thus distinguishing them from localized hypertrophies. Clinically, they are benign. The secondary changes to which they are liable are fatty degeneration of the epithelium, dilatation of the saccules and tubules into cysts, and mucoid softening. As adenomata contain both connective-tissue and epithelial cells, transformation into sarcoma and into carcinoma is possible; the former is more frequent in the young, and the latter in the aged.

Site.—They may develop in any glandular structure or in any tissue containing glandular structure. The chief species of adenoma are: Mammary, sebaceous, thyroid, prostatic, parotid, hepatic, renal, ovarian, testicular, gastric, Fallopian, and uterine. The important varieties of the tumor are the (1) *Acinous;* (2) *tubular.*

1. Acinous Adenoma.—This variety consists of numerous saccules or acini lined with small epithelial cells, which are often two or three layers deep. The acini communicate with one another and are grouped together, being separated by a connective-tissue matrix in which are situated the blood-vessels. The connective-tissue or fibrous stroma varies in amount. Adenoma of the breast is generally seen in young girls at about the age of puberty. The tumor is usually bossed or lobulated, irregular in conformation, and encapsulated. Acinous adenoma is rare, but two cases having come under the author's observation among the hundreds of tumors sent to the laboratory. Fibromata containing more or less glandular structure are not uncommon, and are called **fibroadenomata.** It is often quite impossible to determine whether the gland structure present is newly formed or merely normal breast tissue which has been incorporated in the fibroma.

2. Tubular Adenoma.—This variety is very common in mucous membranes possessing tubular glands. Tubular adenomata are usually

soft, slightly translucent, and somewhat vascular. The tubes are lined with cylindric-cell epithelium. On section, when cut transversely, the tubes appear as circles possessing central lumina and borders of regular cylindric epithelial cells. When cut longitudinally, they often show lateral buds, or even bifurcations, the surface ends of the irregular tubules open on the mucous membrane; at the other end they terminate in blind sacs extending to varying depths; the tubes may be so closely packed together as to show but little fibrous stroma; the cylindric cells lining the tubes are usually two or three times as long as normal. This variety of adenoma is prone to undergo malignant transformation, many of the cancers of the rectum and uterus arising from this tumor.

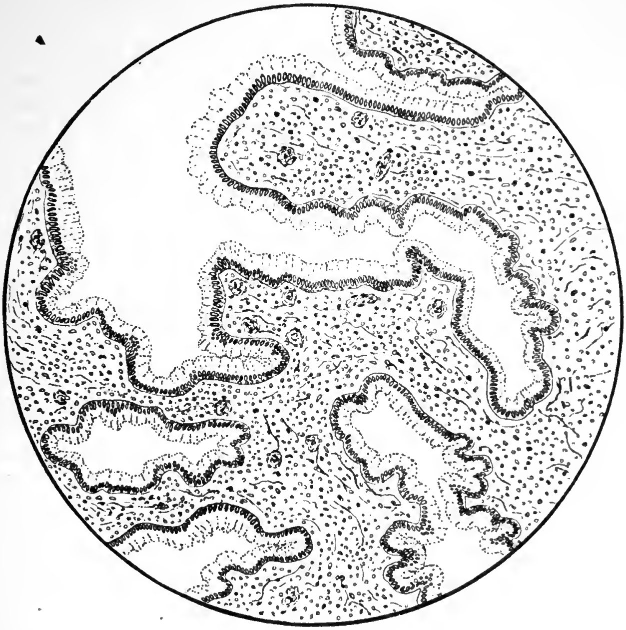


FIG. 167.—ADENOMA OF THE CERVIX UTERI.—(*From a specimen sent to the author by Dr. E. Q. Thornton.*)
The gross specimen was a strawberry-like, pear-shaped mass, 2.5 cm. in length, and attached by a pedicle to the anterior lip of the cervix uteri just at the margin of the os. The tissue was fixed in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin and mounted in balsam. Drawn from $\frac{1}{4}$-inch obj., $\frac{1}{2}$-inch oc. The irregularly formed gland tubules, lined by tall cylindric epithelium, are well shown.

Rectal adenomata are most frequently seen in children, although they may occur at any age. They are strawberry- or raspberry-like tumors, rarely over one or two centimeters in diameter, although the author has had the opportunity to examine such a tumor that was six centimeters in its longest diameter. Most observers have found them multiple; this has not been my experience. The glandular structure imitated is the gland of Lieberkühn. The tendency to transformation into carcinoma (cylindric-cell epithelioma) is remarkable; I have never known a tubular adenoma to persist for any great length of time and escape the change The same is true of a very similar tumor—*adenoma of the cervix uteri.* The great difficulty found in differentiating, histo-

logically, between this tumor and cylindric-cell cancer will be referred to when considering the latter.

III. Neuroma.[1]—A *neuroma* is a tumor consisting almost entirely of nerve tissue; pure neuromata are among the rarest of new growths.

Tumors affecting nerves and not characterized by an increase of the nerve-fibers or cells are called **false neuromata ;** they may be circumscribed or diffuse, single or multiple. Taylor refers to a case in which during thirteen years thirty-two such tumors were removed from the plantar and tibial nerves; more than two thousand have been observed in a single individual. Histologically the nodules may be composed of adipose tissue (*liponeuroma*), myxomatous tissue (*myxoneuroma*), or fibrous tissue (*fibroneuroma*). Sometimes the masses are sarcomatous from the beginning, and in other cases malignancy is developed in structures initially benign.

The **plexiform neuroma** is composed of a series of nodules along the course of a nerve or in a nerve plexus ; at one time this was thought to be a true neuroma; at present it is believed that the new tissue is essentially fibrous, and hence the tumor belongs among the false neuromata or, properly, among the fibromata of nerves. The small multiple fibromata or neuromata of superficial nerves are usually hereditary. The amputation neuromata—which consist usually of fibrous tissue, but which may contain partially regenerated nerve-fibers—form bulbous masses at the cut end of nerves in stumps after amputation, and are intimately connected with the cicatricial tissue of the stump; they are usually painful.

Varieties of Neuroma.—Many tumors found in connection with the nervous system have been shown, with the later improved methods, to contain a quantity of nervous tissue insufficient to justify their special consideration as neoplasms composed of that structure. In theory all true neuromata could be classed under one of three heads: (1) Tumors composed of or containing ganglion cells—*ganglionic neuromata;* (2) tumors made up or composed largely of newly developed medullated fibers—*myelinic neuromata;* (3) tumors composed of or containing evidently newly formed nonmedullated nerve-fibers—*amyelinic neuromata.*

Of the **ganglionic neuromata** but little accurate information is available. Tumors of this kind have been described in the central nervous system and adrenal; they usually consist of a matrix in which there is more or less glia containing ganglion cells. **Myelinic neuromata** affect particularly the peripheral nerves, are frequently multiple, and consist of tortuous myelinic fibrils embedded in a matrix which may be fibrous, myxomatous, or adipose. Divided nerve-trunks sometimes develop nodular enlargements, usually affecting the distal end of the proximal fragment, although Durante reports a case in which the proximal end of the distal fragment was affected. Amputation neuromata belong with this group and are usually thought to depend upon ineffectual efforts at regeneration. Sometimes such tumors are exceedingly painful and particularly influenced by climatic and barometric changes. The **racemose, cirsoid,** or **plexiform neuroma** develops

[1] The exact oncologic position of neoplasms arising from the central nervous system is still a matter not fully determined. Recent researches bearing upon the embryology and histology of the nervous system indicate that neuromata and gliomata may be, for the present, considered with neoplasms of epithelial origin.

as fusiform or nodular enlargements involving particularly the nerve-trunks of the temple, upper eyelid, and back, and occasionally the extremities. Histologically the increase in nerve fibrils is often inconspicuous, the overgrowth being largely in the interstitial tissue, which is sometimes distinctly myxomatous. The tumor is not frequent; Delfosse[1] has been able to collate eighty-eight cases.

IV. Glioma[2] (*Gluey Tumor*, Virchow).—The sustentacular tissue of the central nervous system, according to recent observations, is a derivative of the ectoderm, and, therefore, tumors arising from, or composed of such elements should be classified with the neoplasms of epithelial origin. Gliomata are tumors derived from the sustaining tissue of the central nervous system,—the neuroglia,—and composed of glia cells more or less closely imitating the normal elements. As the glia cell differs at various stages in its development, the adult cell scarcely more than resembling its embryologic ancestor, so differ the cellular elements that enter into the formation of gliomata. In some instances the tumor is made up of cells showing a relatively small number of fibers, comparatively large in size; in other tumors the fibers are particularly abundant. With regard to the size of the cell, it may be small, large, or even approaching the dimensions of a giant-cell. Again, tumors occur that appear to be appropriately classed with the gliomata, and in which the cells more closely resemble ependyma cells. For this class of tumors Flexner has proposed the name *ependyma-cell glioma*. Gliomata are sometimes found containing cellular elements indistinguishable from the cells found in small round-cell sarcoma, and, unfortunately, to such tumors the name **gliosarcoma** has been given. Tumors of this type are most frequent in the eye, apparently originating from the retina. That some of them are true sarcomata is indicated by their occurrence in the young (children from two to six years); by their extension in continuous structures, such as the optic nerve, and by the involvement of the contiguous tissues; not uncommonly they produce fungoid masses, which project from the orbit; and they often recur after removal. Gliomata of the brain do not involve the membranes;

FIG. 168.—FUSIFORM MYXONEUROMA OF THE EXTERNAL POPLITEAL NERVE. (DISSECTING ROOM SPECIMEN.)

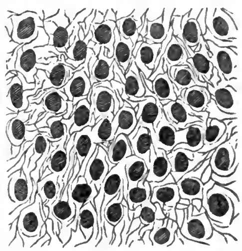


FIG. 169.—GLIOMA.—(*Gould.*

[1] Thèse de Lille, 1904, full bibliography.

[2] LaGrange, "Bulletin de l'Acad. de Méd. Paris," April 2, 1901. Newton, "Australasian Med. Gazette," May, 1902. Holmes, "Jour. Amer. Med. Assoc.," March 28, 1903, p. 821. Bonome, "Virchow's Arch.," 1901, vol. clxiii, p. 441. Mouratoff, "Russki Arkhiv Patologii," etc., June 30, 1902. Pusey, "Trans. Chicago Path. Soc.," Nov. 11, 1901, p. 22; also "Johns Hopkins Hospital Bulletin," October, 1902, vol. xiii. Mallory, "Jour. Med. Research," June, 1902, p. 1; also "Jour. Med. Research," Jan., 1905. Muthmann and Saurbeck, "Ziegler's Beitr.," 1903, vol. 34, p. 445.

sarcomata do. Glioma contains, in nearly all instances, medullated nerve-fibers; sarcoma rarely.[1]

Gliomata appear as more or less circumscribed or slightly diffuse tumors of the central nervous system. As already indicated, their consistency is largely dependent upon the character of the cellular elements that enter into their formation. Occasionally, the tumor may be so soft that it can be handled only with difficulty; in other instances it is firm, and even elastic. The color is dependent upon the amount of blood present and upon the presence or absence of hemorrhage or of degenerative change. Areas of softening or even of cyst formation are occasionally present. Sometimes these cysts show an epithelial lining, the cells of which resemble those forming the wall of the central canal. Commonly, but a single tumor is present; in rare instances, however, the tumor may be primarily multiple, and in still other cases tumors evidently of different ages may be found. In a pure glioma metastasis apparently does not occur. When rapid growth and metastasis are present, the tumor is probably a sarcoma.

Site.—Brain and cord; optic nerve and retina; olfactory lobe.

Embryonic Epithelial Tumors.

Carcinomata, or cancers, are embryonic or atypical neoplasms that always develop from *epithelial* cells. In tumors belonging to this group two essential elements must be recognized: (1) the *cells;* (2) the *stroma*, which bounds the space in which the epithelial cells lie, the space being known as the *alveolus*.

The *cells* are characterized by every diversity of outline; they may be round, oval, squamous, fusiform, cylindric, or caudate, and commonly possess prominent nuclei and nucleoli. The nuclei may be single or multiple, but are always large and usually are characterized by strong affinities for the basic dyes. Variation in the form of the cell is influenced by the pressure to which it is subjected within the alveolus and to the shape of the cell from which the cancer arose. The cells are loosely nested in the alveoli, and do not attach themselves to the contiguous fibrous tissue.

The amount of *fibrous stroma* varies: it consists of distinctly fibrillated tissue, arranged so as to form irregular spaces, called *alveoli*, which communicate with one another, thereby producing a continuous cavernous system, within which the epithelial cells are found. The character of the stroma depends largely on the rate of growth. If rapid, it usually contains round and spindle-shaped cells; if the growth has been slow, or has ceased altogether, the number of formative cells is small and the fibrils coarse and abundant. The latter is the most common condition in scirrhus, the former in encephaloid cancer. The stroma not uncommonly contains a varying number of unstriped muscle-cells, or other histologic elements of the tissue in which the neoplasm is developing. The stroma of uterine cancer is particularly rich in involuntary muscle-fibers, and cancer involving bone may show areas of osseous structure. The blood-vessels are limited to the stroma, and do not pass into the alveoli or communicate with the cavities containing

[1] For the stain and differentiation of glia elements see article on Central Nervous System, in Part III.

the epithelial masses; they have distinct walls that are not infrequently thickened. The lymphatics are probably continuous with the alveoli, which fact accounts for the frequency with which the lymph-nodes are affected. It is principally through these channels that carcinoma spreads. The alveoli were originally lymph-spaces, and therefore communicated directly with the primitive lymphatic ducts draining the area. This communication is not interfered with by the growth of the cancer, but is probably facilitated by the distention of the primitive lymph-vessels by the epithelial cells. As already indicated, the epithelium may readily pass onward, entering the small lymphatic ducts, and later the larger ducts, and eventually the lymph-node or node chain

FIG. 170.—SCIRRHOUS CARCINOMA OF MAMMA.

A. Scanty stroma separating two alveoli. In the upper right and lower left parts of the field the extensive lymphoid and plasma cell infiltration of the stroma is well shown. B, B, B. Cells showing atypic mitoses. C. Cells showing fusion of the protoplasm; formation of the so-called giant cells of cancer. (Technic: Tissue fixed in Heidenhain's corrosive sublimate, paraffin infiltration, hematoxylin, and Van Gieson. B. and L. 1/8-inch obj., 1-inch oc.)

lying between the carcinomatous area and the lymphatic duct that empties into the vein. The extension of cancer along the course of nerves—as, for example, the inferior dental nerve—or along vascular trunks is probably due to the presence of lymph paths that follow the course of the vessel or nerve sheath. By some authors, however, it is considered as a distinct form or method of cancerous extension.[1]

Clinical Characters.—A most interesting fact with regard to some cancers is the existence of a period, preceding the frankly neoplastic growth, in which certain tissue alterations occur constituting what are

[1] See Cheatle, "Brit. Med. Jour.," Dec. 12, 1903, p. 1515.

sometimes called **precancerous manifestations.**[1] Cancer of the mamma may be preceded by eczema of the nipple or cystic changes in the gland substance; lingual carcinoma often follows a prolonged leukoplakia, and similar hyperkeratoses of the prepuce, vulva, cervix uteri, and other mucosæ are not infrequent forerunners of epithelioma. Butlin says that cancer of the tongue is usually preceded by elaborate preparations that clinically may be recognized with a fair degree of accuracy. Chronic ulcerative processes—skin ulcers, gastric ulcer, erosions of the uterine cervix—not uncommonly end in carcinoma, but such conditions are not usually classed with the precancerous manifestations.

As a rule, carcinoma occurs after the age of thirty-five. Over fifty per cent. of all cancerous growths develop after the forty-fifth year. The age of the patient is not so important as the evident age of the structures involved. Thus, the author has seen a well-formed scirrhus of the breast in a patient of twenty-two. The mamma involved, as well as its fellow of the opposite side, showed distinct atrophic changes. The diseased mamma was removed, the tumor did not return, and the patient passed the menopause at thirty. Such individuals are aging prematurely, and in the diagnosis of cancer such factors must be taken into consideration. The growth is usually primarily single, although Warthin[2] records two cases in which the growth was multiple, and has been able to find a number of more or less fully reported instances. Generally, the tumor is hard. The so-called soft cancers are those that have undergone some secondary change, as fatty or colloid, or are made up of epithelium in excess, as the encephaloid. Cancers tend to infiltrate adjacent connective tissues. There is usually a central tumor mass, from which processes radiate into the surrounding tissue. Although it may appear circumscribed, the border of the tissue is never sharply defined; the typical connective-tissue and epithelial-tissue tumors, on the other hand, are likely to have well-defined margins, and, in most instances, can be enucleated from the tissues in which they lie. Carcinoma has no capsule and can not be enucleated.

Secondary carcinoma is usually multiple, possesses a more sharply defined or circumscribed border, and, while it projects into the neighboring tissues, does not tend to infiltrate them with the same rapidity as did the primary tumor; as a rule, the mass is much softer. These characteristics are probably due to the recent and rapid growth of the neoplasm.

Secondary Changes.—The most important are certain forms of degenerative change, among which is fatty degeneration. This depends somewhat on the rate of the growth; the more rapid the growth, the more rapidly this change takes place; hence it is usually most marked in encephaloid cancer. *Colloid degeneration* of the alveolar contents and *myxomatous degeneration* of the connective-tissue stroma are occasionally observed. These processes are particularly marked in carcinomata involving the stomach. *Pigmentation*, or *melanosis* (melanotic cancer), is rare. Calcific deposit, or even true bone formation, may occur; they are, however, quite infrequent. The cysts occasionally formed in cancer

[1] Hartzell, "Jour. of Cutaneous Diseases," Sept., 1903; also Fink, "Cancer and Precancerous Changes," London, 1903; Robson, "Lancet," Dec. 3, 1904, p. 1545.

[2] "Jour. Amer. Med. Assoc.," May, 1899, p. 963.

arise as the result of liquefaction necrosis or of degenerative changes in the cellular elements, or, probably, in most instances, are dependent upon the presence of cysts prior to the carcinomatous development. The contents of such cysts may be fluid, mucoid, or colloid material, and, in rare instances, they may contain more or less blood; the extravasated blood may undergo degenerative and necrotic changes, leaving little of the normal constituents, except the altered brownish pigment, to be recognized. Small areas of hemorrhage into the stroma are not so infrequent, and when ulcerative processes have exposed the surfaces, or when associated necrosis and infection are present,—as in cancers of the uterus and stomach, and occasionally in cancer of the mammary gland,—hemorrhage may be severe and even fatal. The size of the cancer often bears no relation to the amount of hemorrhage, the latter being apparently dependent upon the size of the vessels involved, and possibly, to a less degree, upon the activity of the infective processes.

Various inflammations[1] and infections occur in carcinomatous tissue. After solution in the continuity of the superficial covering, infection may be marked, and the systemic phenomena of sepsis may interfere with the general nutrition, sometimes demanding operative procedures in cancers the extent of which precludes the possibility of complete removal The associated infections are usually pyogenic. Numbers of saprophytic organisms may be present. Tuberculous[2] processes, for example, in the esophagus or larynx may become carcinomatous, or an ulcerating carcinoma may be infected by tubercle bacilli. Tuberculosis and associated cancer of the skin have been observed, and lesions apparently primarily syphilitic, have become cancerous. Evidences of gumma formation in cancer are less frequent, if ever present. Distinct abscess formation in the interior of carcinomatous masses is uncommon. Necrotic processes, and even extensive gangrene, may at times be observed.

Site.—The presence of epithelium being the essential requisite, any surface, tissue, or organ in which this element is present may become carcinomatous. To a certain extent the various forms of epithelium seem to influence the occurrence of different varieties of cancer. The cause of this influence will become more evident as we proceed with the consideration of the forms of carcinoma.

Varieties.—(I) *Epithelial carcinoma* or *epithelioma;* (II) *glandular carcinoma.*

The term epithelioma is used in a broad sense by some writers as referring to all carcinomata. It is here applied to those varieties of carcinoma that usually spring from epithelial surfaces, and is often spoken of as *superficial cancer.*

I. Epithelioma assumes three important types: (*1*) *Squamous;* (*2*) *cylindric-cell;* (*3*) *tubulated.*

1. Squamous Epithelioma.—This variety always grows from surfaces covered by squamous epithelium, either cutaneous or mucous; its epithelial elements closely resemble squamous epithelium; the distortion in shape of the cell is due to the pressure to which it is subjected during its growth. The cells penetrate from the surface epithelium into the lymph-spaces of the connective tissue, and follow those channels that intercommunicate. Occasionally, single isolated epithelial cells may be recognized in the con-

[1] See Cornil, "Rev. de Chir.," April 10, 1904, p. 661.
[2] See Moak, "Jour. of Med. Research," June, 1902, p. 128. Bibliography.

nective-tissue of the growth. Transverse sections of the epithelial masses show typical nesting of cells—the so-called *concentric globes* or *epithelial nests.* When these nests undergo hardening,—a change incident to age and keratinization,—they are spoken of as "*pearls*," hence the term *pearl epithelioma.* These yellowish spherules, composed of cornified or keratinized epithelium, are commonly microscopic bodies situated within the alveolar contents, and showing a marked affinity for acid dyes, notably for the picric acid stains. In rare instances they may be large enough to be seen with the naked eye. The author possesses one specimen of this kind. The diagnostic importance of such bodies (they were at one time held to be pathognomonic) is lessened by their occurrence in other conditions associated with inflammation of the skin; they are occasionally seen at the margins of ulcerative processes that evidently are not cancers, and are prone to occur at the edges of the granulating tissue around ingrowing nails and in onychitis. The fibrous stroma may be the seat of some inflammatory infiltration, particularly if the ulceration incident to softening and infection has occurred. It shows little of the alveolar arrangement that characterizes some of the other varieties of carcinoma. The ulceration, which occasionally occurs early, may not be due to inflammatory or infective processes, as is usually the case, but to necrosis and degeneration of the epithelium.

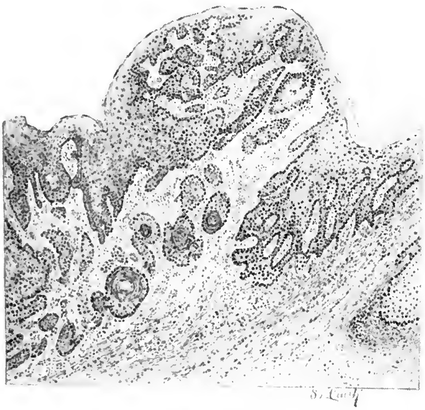


FIG. 171.—SQUAMOUS EPITHELIOMA.

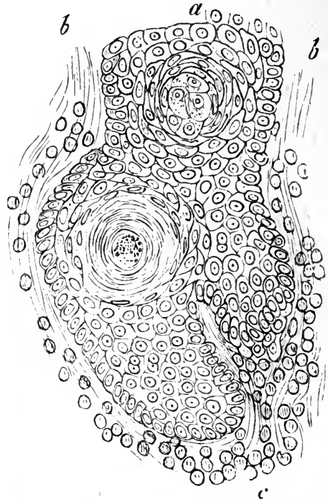


FIG. 172.—SECTION OF A SQUAMOUS EPITHELIOMA.—(*Rindfleish.*) × 500 diameters.
a. The down-growing epithelium in which are two cell nests or pearls. *b, b.* The stroma, in which at *c*, a few lymphoid cells are to be seen.

The growth usually begins as a small nodule, situated in the connective tissue just under the epithelial layer, with which it is continuous; the skin is not movable over the indurated mass. Not uncommonly the spot of induration may appear to be in the epithelial layer. As a rule, the overlying epithelium is pushed upward, giving rise to moderate elevation; this indurated elevation may show slight umbilication, due to fatty changes, absorption, and shrinking in its interior, before superficial exfoliation or ulceration occurs. When fully developed, the cancerous surface presents an irregular, ulcerated, warty appearance. and at times exudes a clear, or slightly tinged, or, it may be, an irrita

ting, ichorous fluid. The ulceration occurs in the center, surrounded by an indurated margin, beyond which may be firm and distinct nodules. There is often a distinct tendency toward incrustation, or scabbing, particularly when situated on the general cutaneous surface, the lip, and at other mucocutaneous junctions. The scab remains attached for a varying length of time, and then falls off or is removed by the patient; after its removal the underlying cancer, just described, is seen to be slightly larger than before the scab formed. This gradual increase in the size of the cancer, observable after each exfoliation of the scab,

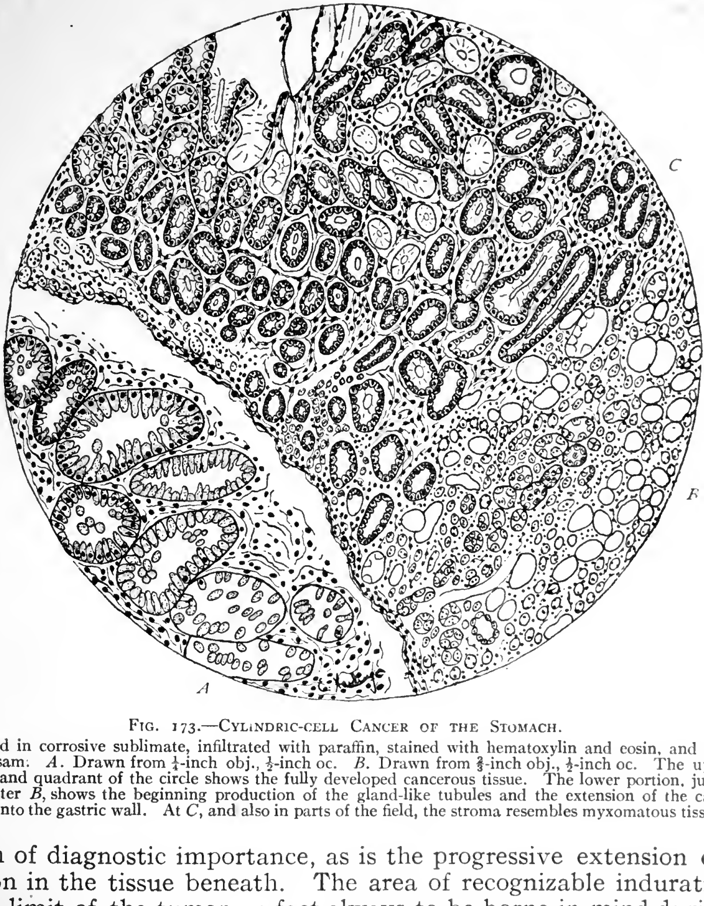


FIG. 173.—CYLINDRIC-CELL CANCER OF THE STOMACH.
Tissue fixed in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin, and mounted in balsam. *A*. Drawn from $\frac{1}{4}$-inch obj., $\frac{1}{2}$-inch oc. *B*. Drawn from $\frac{2}{3}$-inch obj., $\frac{1}{2}$-inch oc. The upper and right-hand quadrant of the circle shows the fully developed cancerous tissue. The lower portion, just above the letter *B*, shows the beginning production of the gland-like tubules and the extension of the cancerous tissue into the gastric wall. At *C*, and also in parts of the field, the stroma resembles myxomatous tissue.

is often of diagnostic importance, as is the progressive extension of induration in the tissue beneath. The area of recognizable induration is not the limit of the tumor—a fact always to be borne in mind during its removal. On section, the tumor is firm, and the fibrous stroma may be seen as white glistening bands. As a rule, there is no hemorrhage; there are few blood-vessels near the surface. The process develops slowly, and glandular involvement may not occur for years, although in rare instances it has been observed within the first year

Site.—Squamous epithelioma usually occurs at the junction of skin and mucous membrane, or where two kinds of epithelium come

together. It is frequently found on the lower lip, nose, penis, scrotum, vulva, anus, and tongue; less commonly on the gums, palate, tonsils, larynx, pharynx, esophagus, bladder, os uteri, and general cutaneous surface; rarely on the hands and feet.

2. **Cylindric-cell Epithelioma** (*Adenoid Cancer, Columnar-cell Epithelioma, Malignant Adenoma*).—This variety of cancer is characterized by irregular or tubular cavities, paved with one or more layers of cylindric cells, and separated by a stroma, which may be fibrous, embryonic, or mucoid. In structure it is said to occupy a position intermediate

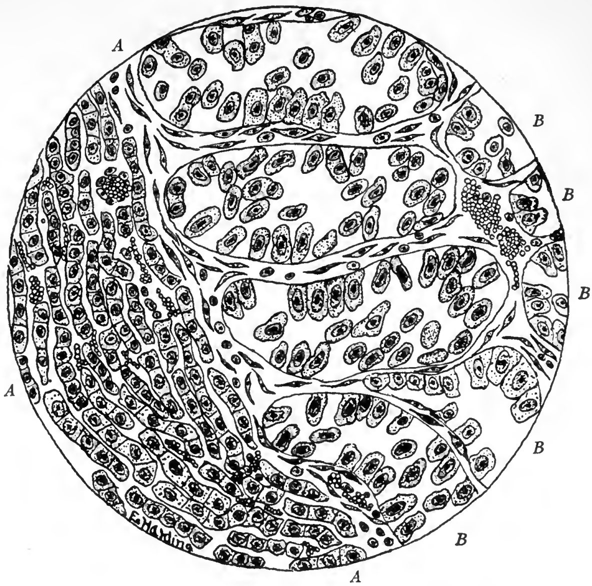


FIG. 174.—SECTION OF CYLINDRIC-CELL CARCINOMA OF THE LIVER.

Tissue fixed in corrosive sublimate, infiltrated with paraffin, stained with toluidin-blue and eosin, and mounted in balsam. Drawn from $\frac{1}{6}$-inch obj., $\frac{1}{2}$-inch oc. *A, A, A*. The liver tissue adjacent to the tumor. The remainder of the field consists of three complete and five incomplete alveoli. Two of the complete alveoli occupy the central portion of the drawing, while the third alveolus (practically complete) is in the extreme upper portion. The parts of alveoli are indicated by the letters *B, B, B, B, B*. About one centimeter inward, and to the left of the second *B* from above, a small area of hemorrhage is present. A similar but smaller area of hemorrhage is seen just below the lower alveolus. The section was taken from a primary cancer of the liver, which showed, in some areas, a structure closely resembling the cylindric-cell cancer; in other areas the absence of any intra-alveolar arrangement of the cells leads to an encephaloid appearance. It will be noticed that in the alveoli shown there is not the characteristic cylindric arrangement of the cells to be seen in figure 173. At some points, however, there is seen a distinct attempt at such an arrangement. The absence of any capsule, or of any effort at capsule formation, between the tumor and the adjacent liver-tissue is well shown. An illustration showing the gross appearance of this tumor is to be found in the chapter on the Liver. Part III.

between the simple adenoma and true cancer. The cylindric cells are similar to those that cover certain mucous or glandular cavities, and are always implanted more or less perpendicularly to the wall. The epithelial elements are similar to those of the mucous membrane from which they grow, but differ microscopically from the arrangement in the normal mucosa in the absence of a basement membrane (membrana propria). The slower the growth, the more nearly typical is the attempted gland formation; in rapid growths and recurrences the cells are small and the lumina imperfect.

Cylindric-cell carcinomata are soft, and are often gelatinous in consistence. On section, they may present a gelatinoid, watery appearance. The rate of growth varies in different cases, and often within wide limits; it is usually rapid, but may be slow. Glandular involvement, or metastasis, usually occurs early and progresses rapidly. In cylindric-cell cancer of that portion of the alimentary canal drained by the portal vein metastasis to the liver is common. Uterine and other forms of pelvic cancer may be similarly disseminated. Cylindric-cell epithelioma, as a rule, occurs in younger patients than does any other variety of epithelioma.

These tumors are usually primary in the rectum (rectal carcinoma may occur very early in life), stomach, uterus, ovary, gall-bladder, liver and biliary passages, or respiratory tract; cylindric-cell cancer may occur in any portion of the intestine. As secondary growths this variety of cancer occurs in the lymphatic nodes, liver, lungs, and kidney, and in bone. The secondary nodules possess the same characters as the primary growth.

The most common forms of degenerative change are mucoid and colloid.

As already remarked, cylindric-cell cancer resembles very closely the tubular adenoma. (See p. 318.) The very close resemblance of the two varieties of tumor has led observers to regard them as possibly identical; the structural difficulty has been concealed by associating with it the clinical phenomena; thus, we find in the German literature constant reference to simple adenoma and to malignant adenoma, meaning by the former the tubulated adenoma, and by the latter the cylindric-cell cancer at present under consideration. It is evident, clinically, that the two tumors are not identical. The small, strawberry-like polyp of the rectum, in children, never recurs after removal, and of the many specimens of simple adenoma of the cervix uteri that the author has seen, none has recurred if removed early in life. In tracing the cases of clearly marked cylindric-cell cancer not a single instance has occurred in which recurrence did not take place in the course of time. Sometimes the newly formed tubules are surrounded by a distinct membrana propria; such a tumor must evidently be a simple adenoma. In the typical tubules of the cylindric-cell cancer no basement membrane is ever demonstrable; in the cancer there is more lawless, purposeless, irregular distribution of the gland-like epithelial cells, and usually a sufficiently prolonged search will show areas so clearly cancerous that the diagnosis can not be doubted. That the simple adenoma may be converted into the cancerous tumor there can be no doubt. Admitting this possibility, it must be conceded that intermediate structural gradations occur, and that occasionally tumors are found in which, from the examination of a single slide, it is quite impossible to state definitely whether that particular neoplasm is simple or malignant. Recognizing that adenoma of this kind is likely to become, without any apparent reason, malignant adenoma, it seems to the author that the method of treatment of such cases is at once simplified—the dangerous character of all doubtful growths of this kind should be admitted, and, in the absence of positive knowledge to the contrary, they should be treated as cancer.

3. **Tubulated Epithelioma** (also variously known as *Rodent Ulcer*,

Tubular Epithelioma, Noli me tangere, Lupus Exedens, Herpes Exedens, etc.).—This form of epithelioma is composed of irregular pavement epithelium arranged in plugs or cylinders that anastomose with one another and are embedded in a stroma consisting of connective tissue, which may be embryonic, mucoid, or, more commonly, dense and fibrous. When mucoid, it is more likely to undergo further degeneration and to become cystic. The epithelial nests and pearls seen in the squamous epithelioma are absent. In some instances the histologic arrangement resembles scirrhus.

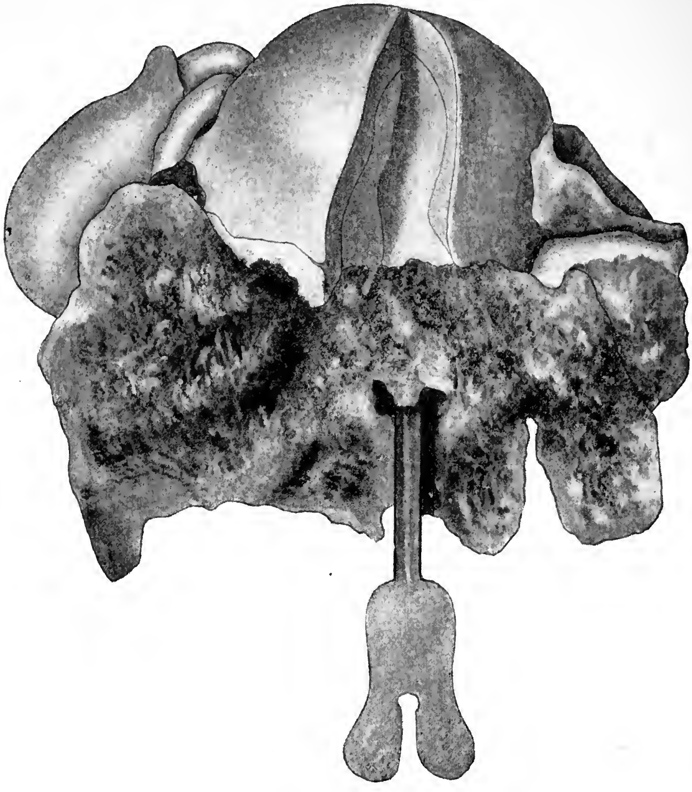


FIG. 175.—CYLINDRIC-CELL EPITHELIOMA OF THE CERVIX UTERI.
The cervix and most of the body of the uterus have been destroyed by the necrotic process. The grooved director shown in position, passes through a perforation into Douglas' pouch. The ovary shown on the left is much enlarged, and is apparently invaded at its point of attachment to the uterus behind. The vaginal vault and the posterior bladder wall have been destroyed.

With regard to the gross appearance and development of this tumor, descriptions have been given that evidently include true lupus (cutaneous tuberculosis). The resemblance is often striking, and a microscopic examination is, in most instances, necessary to differentiate between the two conditions. Tubulated epithelioma occurs in the aged; it appears on the mucous membranes earlier in life than on the cutaneous surfaces. The majority of cases coming under the author's observation

have begun on the lower eyelid or nose. Ulceration appears early, but progresses very slowly, and the process may remain stationary for months, or even for years. The edges of the ulcer are usually elevated, irregular. and indurated. The degree of induration depends largely upon the duration of the process. In old, slowly extending ulceration the induration is more marked than in rapidly progressing lesions. Instances are not infrequent in which partial healing of the ulceration has taken place, and in which, after a variable period of quiescence, extension has been resumed. Sometimes, without any discernible cause, the growth suddenly assumes remarkable activity, and in a comparatively short time shows extensive involvement of adjacent tissues. The author recalls a case in which a tumor developed on the lower eyelid as a small ulceration, ovoid in outline, and, after three years, its diameter did not exceed 0.5 cm. It was excised and its cancerous nature was satisfactorily determined by microscopic examination. Within a year a small recurrent lesion appeared at the site of excision, which, in five years, showed but little tendency toward extension. The tumor then began active growth, and inside of two months had involved the entire lower eyelid and part of the cheek, and had almost entirely destroyed the eye. Excision was again attempted, but seemed to exert but little influence on the rapidity with which the cancer extended.

Glandular involvement is more uncertain in these cases than in any other variety of cancer; in some instances the spread is rapid; in others, slow; in some cases it does not appear at all. When upon the mucous surfaces, or upon the eyelid, the growth is frequently rapid.

Krompecher[1] describes a group of tumors believed to arise from the basal cells of the Malpighian layer of the skin, resembling, in some respects, other forms of cutaneous epithelioma, and called **carcinoma basocellulare.** In Emley's series of 35 cases, 24 of the patients were males, 21 were over fifty years of age; only one patient was under twenty years. The average duration was over eight years, and in none of the cases was there involvement of the lymph-nodes. The tumor cells are continuous with the Malpighian layer and may be collected in groups—*bulbous form*—surrounded by narrow bands of mature fibrous stroma. In other instances—*cystic form*—small cavities containing turbid fluid are present; usually the wall of such spaces is formed by tumor cells, but occasionally the connective-tissue stroma may be exposed. In another group of these neoplasms the epithelium extends as irregular branching projections resembling the tubulated epithelioma referred to above; this type Emley terms the *styloid form.* The fact that these basal cell cancers are materially different from other forms of carcinoma is shown by the occurrence of encapsulation and by their usual benignancy.

Site.—The most frequent location is on the face, tongue, and general cutaneous surface. A similar but certainly not identical neoplasm is occasionally seen in the intestine, uterus, and ovary. When occurring in the skin, the mass is believed to develop from the sweat-glands, or, possibly, from the hair-sheaths.

[1] "Ziegler's Beitr.," 1900, Bd. xxviii. See also Emley, "Trans. of the Chicago Path. Soc.," 1904, vol. vi.

II. Glandular Carcinoma.—*Varieties.*—(*1*) *Scirrhus;* (*2*) *encephaloid carcinoma.*

1. Scirrhus (*Acinous Cancer, Chronic Cancer, Hard Cancer, Fibrous Carcinoma*).—This variety of carcinoma is characterized by the abundance and density of its stroma and by its irregular growth. The tumor occurs as a hard, firm mass, varying in appearance according to its location. In the mamma, which is its usual site, it forms a hard, rounded or irregular mass, which soon becomes firmly attached to the subcutaneous tissue, and eventually to the skin. By the contraction of the fibrous stroma it causes retraction of the nipple and puckering or dimpling of the skin—"bacon-rind" skin. (See Figs. 176 and 177.)

On section, it presents a grayish-white glistening appearance, dotted with yellow patches of fatty tissue. The fibrous bands and fatty areas

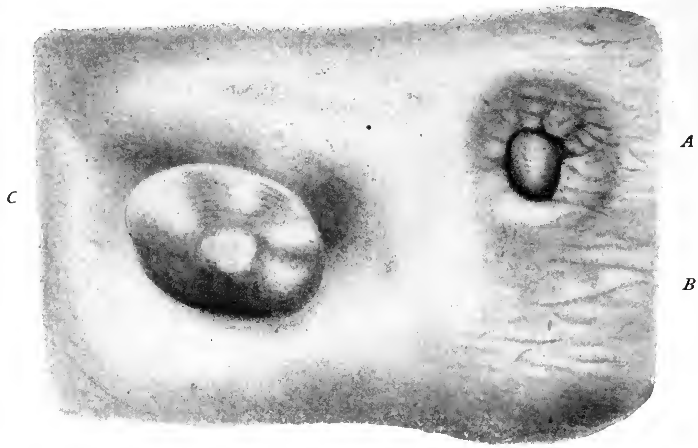


FIG. 176.—PART OF CUTANEOUS SURFACE OF RIGHT MAMMA THE SEAT OF A CENTRALLY PLACED PRIMARY SCIRRHOUS CARCINOMA AND OF A SECONDARY NODULE

Just to the left of the letter *A* is the nipple, showing the retraction or umbilication, with puckering or dimpling of the skin of the surrounding areola. The "bacon-rind" appearance is even more marked just to the left of *B*. To the right of *C* is a secondary nodule, firmly attached to the skin, which is drawn in around the neoplasm; the surface of the nodule shows the stretched skin which at the five pale ovoid or irregular areas is greatly thinned.

are more marked near the center of the tumor. Toward the periphery it is more vascular and less fibrous; it is nonencapsulated. On microscopic section, the tissue is composed of two structures, connective tissue and epithelial cells, the connective tissue or stroma being arranged so as to form a series of rounded or irregular spaces (alveoli) in which the epithelial cells are nested. The blood-vessel walls are thickened and fibrous. Microscopic sections from the central part of the tumor will show the connective tissue more dense and fibrous and the alveoli much smaller, with the epithelial cells small and atrophied, or possibly degenerated. With the increase in the fibrous stroma there is increased contraction, causing irregularities of the surface; when occurring in the breast, this contraction gives rise to retraction of the nipple—umbilication.

During the development of the morbid process contraction of the fibrous tissues may be more rapid than epithelial proliferation, and the organ involved—for example, the breast—may actually diminish in size with progressive induration; when this contraction is marked, the tumor is said to be atrophic or "withering." (See Atrophic Scirrhus.) Another diagnostic point depending upon the contraction of the fibrous tissue is the "cupping" of the center of the mass when divided by an equatorial incision; this is not always present, but can usually be demonstrated. If the neoplasm be cut in halves by a clean, smooth incision, the central part of the cut surface of each half retracts, thereby depressing that part of the incised surface below the surrounding margin—the depressed area constituting the so-called "cup." (See Fig. 177.)

Glandular involvement usually takes place within the first year, and is practically always demonstrable by microscopic examination even when not evident to the unaided eye.

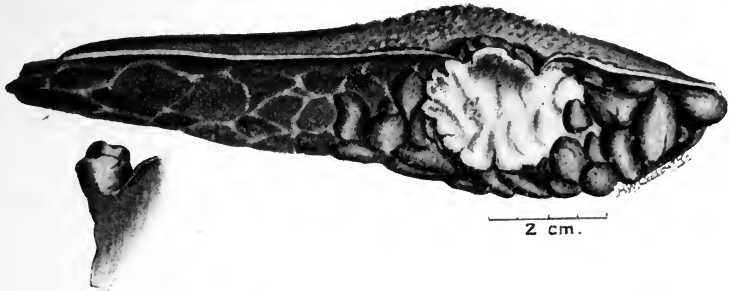


FIG 177.—CARCINOMA OF THE MAMMA; AXIAL SECTION THROUGH THE NIPPLE IN LINE FROM STERNUM TO AXILLA.

The depressed nipple occupies the summit of the center of the cancerous area. The small drawing to the left shows in profile the cupping of the incised surface. (Illustration two-thirds natural size.)

Glandular carcinoma, usually scirrhus, may arise from cystic processes affecting the mammary gland,[1] particularly that morbid condition called cystic disease of the mamma or chronic mastitis associated with the development of cysts. Some sections from the breast studied by Ellis showed that the epithelium lining the cyst cavities was continuous with the cells occupying alveoli of clearly cancerous areas. Such a demonstration calls attention to the manner by which the lining cells of the mammary acini may extend into the connective tissue of the organ, thereby producing carcinoma.

The *forms of degeneration* occasionally seen in hard cancers are fatty, colloid, mucoid, and hyaline, and, rarely, caseous necrosis. Melanotic, or pigmentary, and calcareous infiltrations occur. The most remarkable feature of some of these cases is the spontaneous disappearance of the neoplasm; nodules that have developed after operation (recurrent carcinoma) may cease to grow or even atrophy. There is evidence to

[1] See Ellis, "Publications from the Laboratories of the Jefferson Medical College Hospital," 1904, vol. i, reprint from "Annals of Surgery," Sept., 1903. Bibliography.

show that even visceral metastases may manifest retrogressive changes. Instances illustrating this peculiar phenomenon are exceedingly rare but of undoubted occurrence.[1] It is not known exactly what histologic alterations accompany the disappearance, but probably the changes are similar to those seen in the atrophic scirrhus.

Scirrhous carcinoma is most frequent in the breast, uterus, stomach (pylorus), esophagus, rectum, and kidney; it is rare in ovary, testes, and prostate.

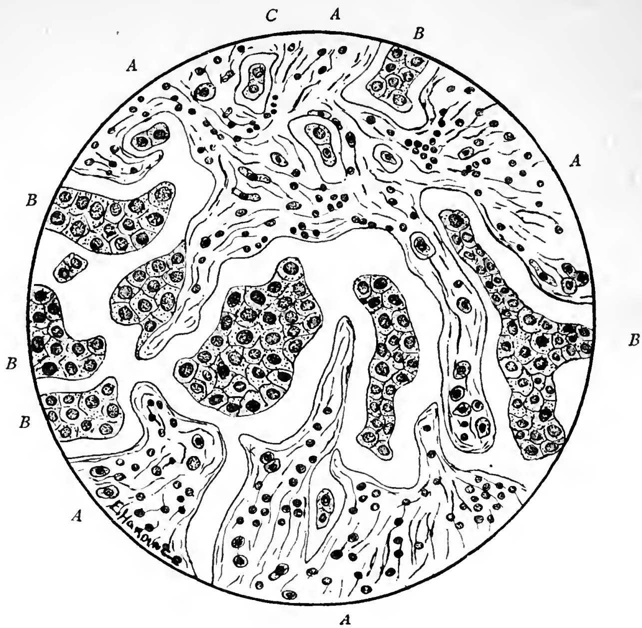


FIG. 178.—GLANDULAR CARCINOMA OF THE LIVER (SCIRRHUS).

Tissue fixed in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin, and mounted in balsam. Drawn from $\frac{1}{6}$-inch obj., $\frac{1}{2}$-inch oc. *A, A, A, A, A.* Connective-tissue stroma. *B, B, B, B, B.* Epithelial cells occupying, but not filling, the alveoli. Communication between the alveoli is well shown, as practically all the large alveoli communicate. Just below *C* is shown a small alveolus containing two epithelial cells, and a little to the right is a similar alveolus. A number of efforts were made to demonstrate that the clear space surrounding the epithelial cells was occupied by some material that would not stain by the method used in the section from which this drawing was made. All efforts to secure such demonstration were futile. It is probable that the space is produced by the contraction of the epithelial cells during the process of fixation or hardening, or that the spaces shown are filled during life with some fluid not coagulable by the fixing method used.

Atrophic Scirrhus.—When the production of fibrous tissue predominates, and the epithelium proliferates but slowly, the resulting tumor contracts much more rapidly than it grows. The epithelial cells are therefore pressed upon, and often disappear from many areas. This form of scirrhus is a breast tumor, and, once developed, it is generally found that the gland and tumor progressively diminish in size. The malignancy is low, and if the fibrous tissue development persists in its excess, the patient rarely succumbs. The writer had a case under

[1] Osler, "Amer. Med.," April, 1901; also Willson, "Brit. Med. Jour.," Dec. 20, 1902, p. 1899.

observation, a woman seventy-two years of age, who had refused an operation nearly twenty years previously. The entire breast of one side, and the overlying and adjacent skin, showed puckering and contraction; the breast of the other side was also invaded, but ulceration had not taken place over either gland. Lymphatic involvement may be long delayed, or, in a few cases, may not occur. In the case just mentioned there was very slight involvement in the last few years only. The patient died at seventy-four, of erysipelas. Microscopically, such tumors are mostly fibrous stroma, with few alveoli; the contained epithelial cells are advancedly atrophied or degenerated, or both.

FIG. 179.—CARCINOMA ARISING IN A MAMMA THE SEAT OF CYSTIC DISEASE.
A. Necrotic detritus contained within a cyst. *B*. Proliferating epithelium lining the cyst. At points this layer shows desquamation into the cyst cavity. *C*, *C*. Two points where the epithelial lining of the cyst is continuous with the epithelium of the alveoli of adjacent carcinomatous tissue. *D*, *D*. Intra-alveolar epithelial nests characteristic of this type of carcinoma.

2. Encephaloid Carcinoma (*Medullary Carcinoma, Soft Cancer, Acute Cancer*).—This infrequent variety of carcinoma is a soft, rapidly growing, brain-like tumor, in which the fibrous stroma is more nearly embryonic, not uncommonly myxomatous, and very scanty; the alveoli are large, and are filled with large, rapidly growing epithelial cells. The tumor appears as a soft, at times almost fluctuating, nodular mass, which tends to ulcerate and to bleed (fungus hematodes). There is early involvement of the skin ("bacon rind"), soon followed by superficial necrosis and ulceration. As a rule, encephaloid carcinoma occurs earlier in life than scirrhus, and has been reported in the young. It

may occur as a primary or secondary growth. The growth is exceedingly rapid, and glandular involvement takes place early—within the first six months. There is no retraction of the nipple when occurring in the breast, and the rapidity of growth produces a more clearly circumscribed mass than scirrhus; it is, however, more rapidly fatal.

Primarily, encephaloid cancer is most common in mammary gland and in testes; it may occur as a secondary growth following scirrhus, particularly when the latter involves the internal organs. Encephaloid cancer is much less common than scirrhus.

Colloid or **gelatiniform carcinoma** is a form of cancer in which degenerative changes take place in the protoplasm of the epithelial cells of the alveoli or in the connective-tissue stroma. The typical colloid cancer belongs to the glandular group, although a similar change is sometimes observed in the cylindric-cell epithelioma, particularly of the liver. The two conditions are, however, by no means identical, and are therefore easily differentiated. Gelatinous transformation of glandular carcinomata occurs frequently in cancer of the intestinal canal,

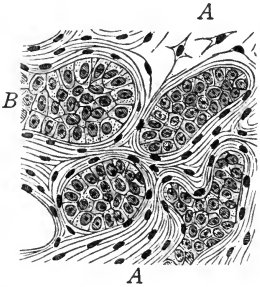


FIG. 180.—ENCEPHALOID CARCINOMA (SOFT CANCER).—(*Gould.*)

A, A. Stroma made up of developing connective tissue. At the upper *A* the stroma is almost myxomatous. *B.* Epithelial cells occupying an alveolus; three other alveoli are shown.

FIG. 181.—GLANDULAR CARCINOMA IN WHICH THE STROMA HAS BEEN CONVERTED INTO MUCOID TISSUE.—(*Gould.*)

Note the stellate cells so closely resembling those seen in myxoma.

particularly of the stomach, and less frequently in cancers of the mammary gland, testes, and ovaries. Gelatinous areas are sometimes found that no longer contain any of the structural elements by which it is possible to identify carcinomatous processes. In the younger parts of the tumor, however, advancing transformation may usually be recognized; a varying number of epithelial cells may be found, centrally placed in the alveolus, and surrounded by concentric lamellæ of gelatinous material. The tumors are soft and trembling, glassy, and at points semitransparent. In the mammary gland metastasis may be delayed; in the stomach rapid extension to the peritoneal surface, and more or less diffuse carcinomatosis of the serous surface, may be rapidly developed. (For the chemistry of colloid and mucoid changes see p. 248.)

Mucoid Carcinoma.—When the substance that distends the alveoli is more viscid in character, it is believed to be the result of mucoid degeneration of the intercellular substance, rather than a colloid change commencing in the cell. It is the transformation of the albuminoid

constituents of the tissue into a complex proteid rich in *mucin*. Until our methods of differentiation become more accurate, and, until we know more of the evolution of mucoid and colloid carcinomata, it would probably be best to consider them both under the head of *gelatinous* or *gelatiniform cancer*.

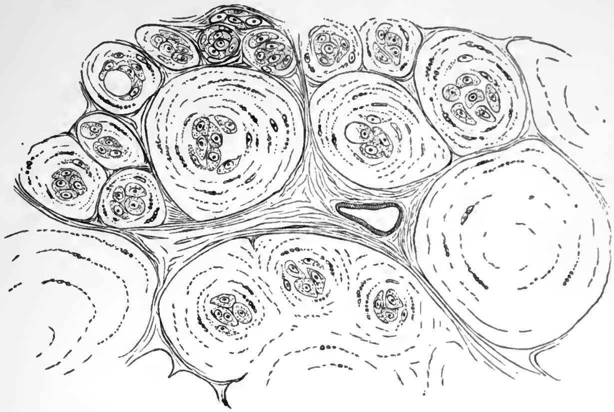


FIG. 182.—COLLOID CANCER.—(*Rindfleisch.*) ×300 diameters.
The stroma has been but little involved, while the intra-alveolar structure has been converted almost entirely into gelatiniform material.

Melanotic carcinoma is, in the writer's experience, a very rare tumor. It is believed that the pigment-forming cells of epithelial origin are present in certain forms of cancer, and that melanosis in such tumors is due to the activity of these cells. Melanotic cancers are usually malignant to a high degree, manifesting a tendency to metastasis early; the secondary nodules are pigmented.

CONNECTIVE-TISSUE TUMORS.

ADULT CONNECTIVE-TISSUE TUMORS.

I. Lipoma or fatty tumor is a localized, more or less circumscribed, new formation of fat. Lipomata are usually lobulated, soft, doughy, pseudofluctuating, and inelastic. As to shape, they are ovoid, spheric, or flat, commonly sessile, rarely pedunculated. If encapsulated, the capsule is exceedingly thin; non-encapsulated fatty tumors are sometimes spoken of as *diffuse lipomata*, the margins being often not clearly defined. Lipomata are rarely multiple[1]; instances, however, occur in which a large number may be present. The author recalls a case in which multiple lipomata situated in the axilla, groin, and neck led to the diagnosis of Hodgkin's disease. The diagnosis in this case was made more difficult by the presence of calcareous infiltration and true bone formation in the interior of the tumors, rendering them more dense and causing a striking resemblance to multiple lymphadenomata. Multiple lipomata are said to occur in families; not infrequently the inherited tendency is transmitted through several generations. Some

[1] Queinnec, Thèse de Paris, 1903.

times the distribution, or even the conformation of the growths is characterized by symmetric development on the two sides of the body. In some of these cases the tumors are of congenital origin. An interesting phenomenon observed in fatty tumors is "gravity wandering"; this feature may be present in tumors developing in the subcutaneous tissues and possessing slight attachment to the surrounding structures. Fatty tumors developing on the upper portion of the chest-wall, near the axilla, or on the back, may, in the course of time, descend to the level of the pelvic brim, and lipomata of the thigh may wander as far as the knee. The distance traveled and the rapidity of movement are, of course, influenced by the amount of attachment and by anatomic relations.

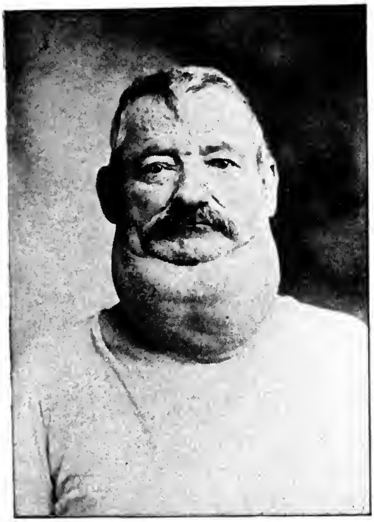


FIG. 183.

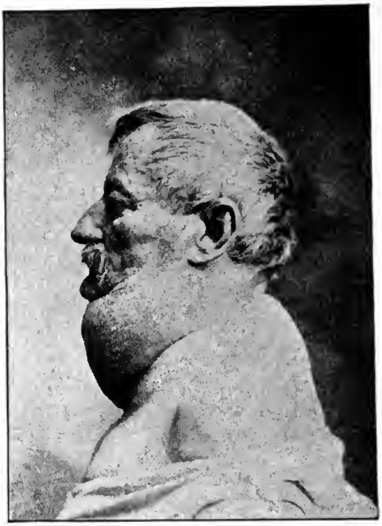


FIG. 184.

DIFFUSE LIPOMA OF THE NECK.
Case reported by Dr. J. Shelton Horsley in the "Philadelphia Medical Journal," July 8 1899 (reproduced by permission).

Microscopically, fatty tumors consist of cells containing fat and of a variable quantity of connective-tissue stroma. The cells are like those of adipose tissue, though usually larger. The blood-vessels are distributed in the fibrous stroma. If the fibrous tissue is in excess, the neoplasm is called a **fibrolipoma,** or fibro-fatty tumor. The fibrous fatty tumor, or fibrolipoma, differs from the **simple lipoma** only in the amount of fibrous tissue that it contains. In the fibrolipoma this is abundant; there is no capsule, and, if the tumor be grasped at its base and the skin made tense, dimpling of the cutaneous covering occurs; this result is brought about by the fibrous bands which traverse the tumor pulling in the skin at their points of attachment. When the periphery of the neoplasm is sharply outlined from the adjacent tissues, the tumor is known as a *circumscribed lipoma; diffuse lipomata* are not encapsulated

and are continuous with the fatty tissues in which they arise. Lipomata containing myxomatous tissue are called *myxolipomata.*

Clinically, lipomata are benign tumors of slow growth and of variable size.

The *infiltrations and degenerations* that they may undergo are calcareous infiltration and mucoid degeneration, ossification, ulceration, and cystic degeneration; secondary inflammatory and necrotic changes also occur.

Lipomata may occur in any connective-tissue. They usually involve the subcutaneous tissue of the trunk, especially of back and abdominal walls, intermuscular septa, subsynovial and subserous tissues. Lipoma is rare in stomach and intestines and other internal organs. Retroperitoneal and mesenteric fatty tumors sometimes become very large and may weigh 15 kilos or more.[1]

II. Chondroma (*Enchondroma, Enchondrosis, Chondroid Exostosis*).—Chondromata are masses of new tissue, composed of hyaline, elastic, or white fibrocartilage. Chondromata developing from preexisting cartilage, such as the cartilages of the larynx and trachea and the costal cartilages, may assume a polypoid shape, and are not uncommonly multiple, and are spoken of as *ecchondromata.* Developing from bone or in tissue not normally containing this element, the cartilaginous tumors are called *enchondromata.* The term *chondroid exostosis* is applied to a cartilaginous tumor growing from bone; such a tumor may appear as a periosteal, subperiosteal, or medullary growth. Cartilaginous tumors are usually rounded, smooth, tuberous, or lobulated masses of very dense consistence; owing to the compression of the surrounding tissues, they often appear to be encapsulated; not uncommonly, however, they possess well-marked capsules. The cut surface presents a pearly, bluish-pink appearance, identical with fresh cartilage. As a rule, cartilaginous tumors are nonvascular; but if vascularization occurs, it is at the center or through the fibrous septa. Tumors composed of cartilage are most frequent in the young, and are rare after puberty.

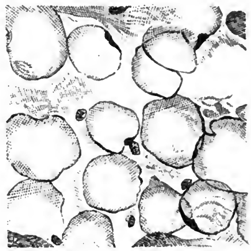


FIG. 185.—LIPOMA.—(*Gould*.) The globular fat-cells with nuclei displaced to the cell margin are well shown.

Microscopically, the cells of the neoplasm resemble those found in true cartilage; the intercellular substance may be hyaline, faintly or distinctly fibrous, or, in rare instances, mucoid. They are not, as a rule, composed of dense cartilaginous tissue, but of islands of cartilage surrounded by fibrous septa. The cartilage matrix is hyaline, except at its junction with the fibrous stroma, where it is usually more or less fibrous. Within the matrix are the lacunæ containing the cartilage cells; these resemble the cells of normal cartilage, except that branching, stellate, and irregular forms are frequently present; usually they are rounded or oval in shape. The lacunæ of the matrix are occasionally branched, so as to cause the appearance of a series of star-shaped spaces, with cartilage cells lying in their centers

[1] See Campbell, "Brit. Med. Jour.," Nov. 28, 1903, p. 1397.
[2] Löwen, "Deut. Zeitsch. f. Chir.," 1904, Bd. lxxv.

Fatty, calcareous, mucoid (most common), and cystic changes sometimes affect cartilage tumors; ossification may occur, especially when the tumor springs from the junction of the epiphysis and shaft of a long bone.

Chondromata are most frequent in tissues that normally contain bone; as bones are developed largely out of cartilage, it may be supposed that remains of this structure are left behind (Cohnheim's rests), and that they afterward develop into tumors. Chondromata occur most frequently on the metacarpal bones and phalanges of the hands; not so frequently on the corresponding bones of the foot. They are not infrequent on the femur and bones of the pelvis, in the last-named situation not uncommonly attaining the largest size; they also occur on the ribs and scapulæ, rarely on the face and skull, sheaths of tendons, and bronchial cartilages. Chondromata are infrequent in the soft parts, but have been observed in the testicles, ovaries, mammæ, and salivary glands. Chondroid and osteoid masses occasionally develop from the inner table of the skull and from points of junction of the cranial bones that normally coalesce. In very rare cases chondroma gives rise to metastases, which may occur in the lungs, spleen, brain, liver, and heart. Michaeloff[1] collected 14 such cases.

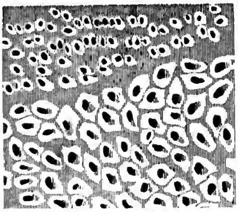


FIG. 186.—CHONDROMA.—(*Gould.*)

III. Osteoma.—A tumor-like mass of bone developed without the occurrence of inflammation or incident to the process of repair; usually such tumors occur at the point of junction between a bone and contiguous cartilage. Osteomata are classified, according to their position, as (1) **exostoses,** or those growing from the exterior of a bone, and (2) **enostoses,** or those growing from the interior of a bone. According to their structure they are divided into (*1*) *eburnated;* (*2*) *compact;* (*3*) *cancellous* or *spongy.*

1. Eburnated Osteoma.—These occur most frequently on the inner table of the skull, and are not uncommonly of syphilitic origin. They are extremely hard, symmetric, and usually multiple. On section, the dense bony structure is found to be composed of lamellæ, which are arranged parallel with the surface of the tumor. In the lamellæ there are no blood-vessels and no Haversian canals, but canaliculi similar to those found in the cementum of the teeth; these run toward the surface.

2. Compact Osteoma.—This variety is composed of ordinary compact bone, similar to that found in the outer layer of the long bones. Frequently the growth is nodular, usually beneath or in the periosteum, and commonly affects the long bones. On section, it is found to differ from the eburnated osteoma, in that the vessels and Haversian canals run at right angles to the long axis of the bone. The tumor possesses a periosteal fibrous covering, beneath which is a layer of small round cells (osteoblasts); peripheral growth of the osteoma is accomplished through the activity of these cells. Regular Haversian systems may be clearly defined.

3. Cancellous or Spongy Osteoma.—In this variety the trabeculæ are very thin and are not numerous; the medulla is embryonic in character, and often appears as a gelatinous mass. In rare cases it is distinctly

[1] Quoted by Patel, "Rev. de Chir.," March 10, 1904, p. 398.

fibroid. The whole tumor is essentially similar to the spongy tissue of which the ends of long bones and the bodies of shorter ones are composed.

Osteomata are benign tumors of slow growth, usually arrested with advancing age, and rarely attaining a large size. They are often hereditary and multiple, in which case they usually occur in early life. Osseous growths that exhibit malignant characters are *osteosarcomata*, or *sarcomata* that have undergone partial ossification or extensive calcareous infiltration. Osteoma may inflame, become *carious*, or undergo *necrosis*. Rarely such tumors are transformed into sarcomata.

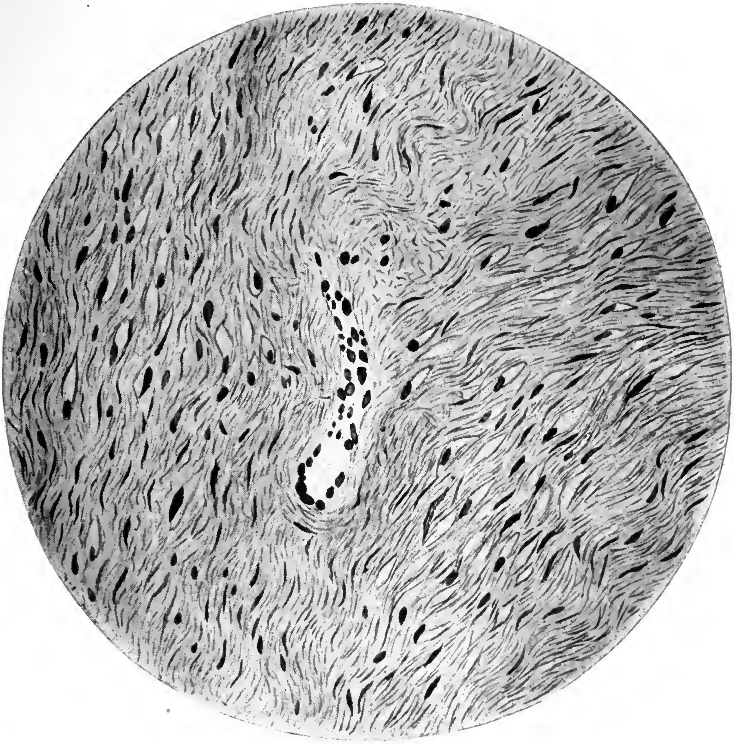


FIG. 187.—SOFT FIBROMA.

Osteomata are most common in connection with periosteum, bone, medulla, or cartilage. They may occur in the soft parts of the body, in the brain substance, in the dura mater and pia mater, in the pleura, diaphragm, pericardium, in the skin, in the choroid coat of the eye, in the air-passages, around or in lymph-nodes, in nerve-centers, and in tendons.

IV. Fibroma (*Fibroid, Desmoid, Steatoma, Inoma*).—Fibromata are tumors composed of wavy bundles of fibrous tissue.

Simple Fibroma.—This variety is typified by the *painful subcutaneous tubercle*, which consists of a nodule about the size of a coffee-bean in

the subcutaneous cellular substance. It is of firm consistence, and is apparently quite circumscribed, being situated loosely in the cellular tissue immediately under the integument. From the extreme pain produced by these small nodules, many have imagined that they must contain nerve-fibers; careful research, however, has in all cases failed to demonstrate the existence of such structures. They occur more frequently in the female than in the male.

By some authorities fibromata are said to be *hard* or *soft*, the density being dependent upon the degree of development. The hard or dense fibroma (*fibroma durum*) is of the type of dense fibrous tissue, while the soft fibroma (*fibroma molle*) is composed of a younger, more cellular growth, containing fewer fibers. The hard fibroma is firm, usually lobulated, and encapsulated The soft fibroma is much less dense, and in texture resembles the lipoma; it may be lobulated and encapsulated. The density of the fibroma upon which the foregoing subdivision is based, may be dependent upon factors other than the developmental stage of the fibrous element. Myxomatous transformation of the intracellular substance (*myxofibroma*) and edema produce soft, often semifluctuating fibrous masses. In addition to the fibrous tissue, other connective-tissue elements may be present; when such elements are sufficiently abundant, the condition is indicated in the following manner: For fatty tissue, *lipomatous fibroma*, or *fibroma lipomatodes;* for bony tissue, *ossifying fibroma*, or *fibroma ossificum;* a fibroma rich in capillaries is called *angiofibroma* or *telangiectatic fibroma*, or *fibroma telangiectaticum.*

FIG. 188.—NEUROFIBROMATOSIS.—(*Pode.*)

Neurofibromatosis[1] or **Molluscum Fibrosum** (*Fibrocellular Tumor, Dermatolysis, Pachydermatocele*).—This variety of fibroma is a rather extraordinary condition, the chief feature of which is an overgrowth, apparently not inflammatory, of the fibrous structure of the nerves, particularly those situated in the skin and subcutaneous tissues. The new growth may affect a small area, such as the scalp, or it may involve a large extent of skin on the trunk or extremities, or both, causing it to hang in pendulous folds. Sometimes the tumors form as separate nodules scattered over the skin; thousands may be present. Any or all the nerves in the body, except the olfactory and optic, may be affected; the acoustic nerve is frequently involved. The new growth may be within the nerve (endoneural variety) or

[1] Anthony, "Jour. Amer. Med. Assoc.," June 13, 1903, p. 1630. See also "Johns Hopkins Hospital Bulletin," vol. xiv, p. 204. Rudler, "Nouvelle iconographie de la Salpêtrière," May and June, 1904, vol. xvii. Abbott and Shattock, "Trans. Path. Soc. of London," 1903, vol. 54, p. 231. Fraenkel and Hunt, "Med. Record," June 13, 1903, p. 925. Lion and Gasne, "Bull. de la Soc. des Hôp. de Paris," Jan. 21, 1905, p. 5. Richardson, "Lancet," Dec. 3, 1904, p. 1562. Noyes, "Jour. of Path. and Bact.," Dec., 1903, p. 240.

around the nerve (epineural or perineural variety). Microscopically, the tissue is composed of fibrous bundles with intervening branched cells, the processes of which clasp the bundles. In the dense fibrous bands there are few cells. The cells are, in many instances, almost embryonic in appearance, and the tissue is particularly rich in nuclei. Merken has recently studied fibroma molluscum, and concludes that it depends upon some congenital factor closely allied to that operative in the production of nevus. Some cases have been thought to be sarcomatous. The cause of the condition is unknown; instances of congenital neurofibromatosis have been recorded.

Keloid[1] (*Cheloid*, *Kelis*).—This is a rare variety of fibroma. It takes the form of tuberous, sausage-like, or discoid growths seated in the corium beneath the papillary layer.

True keloid consists of a fibrous growth in the corium, covered with a papillary layer; the papillæ and epidermis are intact. It is most common in the negro. It is composed of bundles of coarse fibers, and in the early stage contains numerous spindle cells. **Cicatricial keloid** develops in the substance of a scar, and differs from the true keloid in that it is not covered by the papillary layer. In other respects it resembles the true keloid.

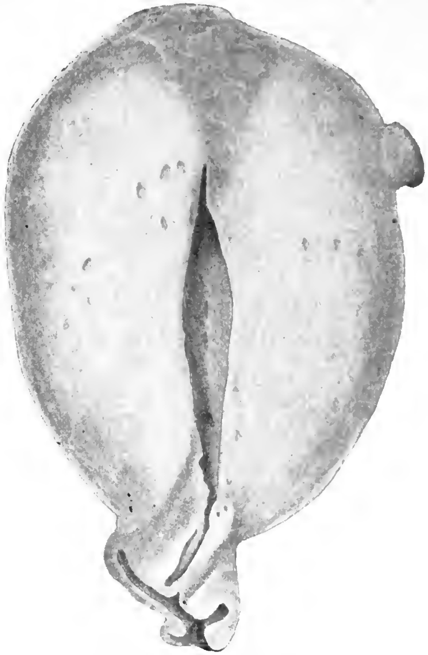


FIG. 189.—SECTION (LONGITUDINAL) OF THE UTERUS, SHOWING UNIFORM MYOMATOUS ENLARGEMENT.

At *A* is a small subserous myoma beginning to form a pedicle. The small depressions shown on the incised surfaces are sections of sinuses, some of which contained thrombi.—(*From a specimen in the museum of the Jefferson Medical College.* The drawing is one-fourth natural size; the artist has slightly exaggerated the transverse diameter of the uterine cavity. Weight of specimen, 5760 gm.)

Fibromata originate in connective tissue, cutis, or subcutaneous tissue, from submucous or subserous tissue, from fascia, periosteum, neurilemma, or the connective tissue of organs (uterus, ovaries, testicles, mammary gland, and labium majus). Clinically, they are benign tumors of slow growth, and, with the exception of keloid, do not tend to recur after removal.

Serous infiltration (as in molluscum fibrosum), mucoid degeneration, fatty degeneration (especially in the simple fibroma of syphilitic origin), calcification (*fibroma petrificum*), suppuration, and ulceration may affect fibromata. A fairly large number of these tumors develop into sarcomata.

V. Myoma.—The myomata are tumors composed of muscle-tissue. Two forms of the myoma are recognized, depending upon the kind of

[1] Ravogli, "Jour. Amer. Med. Assoc.," July 30, 1904, p. 297.

muscle that the tumor simulates. A tumor composed of nonstriated muscle-fiber is called a *leiomyoma*, or *myoma lævicellulare;* a tumor containing a varying amount of striped muscle-fiber has been described, and is called *rhabdomyoma*, or *myoma striocellulare*.

Leiomyomata occur most frequently in the uterus, and not uncommonly contain more fibrous tissue than similar tumors occurring elsewhere. Leiomyomata also occur in the prostate, tongue, esophagus, stomach, and intestines. As a rule, this variety of tumor arises only in situations containing unstriped muscle-fiber. The tumors vary in size. Myomata of the intestinal wall are usually small; myomata of the uterus may attain the size of a fetal head, or, in rare instances, they may be larger; a number of instances have been reported in which the tumor weighed over one hundred pounds. Severanu removed a uterine myoma weighing 195 pounds.[1] Myomata may be *single or multiple*. Multiple myomata—when a number of tumors occupy the same organ—give rise to a mass the surface of which is tuberous, bossed, lobulated, or irregular. Myomata in the intestinal wall may project from the serous surface as distinct, pedunculated tumors. The same condition is possible in the uterus. *Uterine myomata* are said to be *subserous* when situated immediately beneath the peritoneum, *submucous* when located immediately under the mucous membrane, *interstitial*, or *intramural*, when more or less centrally placed in the uterine wall. Most authorities agree that all uterine myomata begin as interstitial, or intramural, growths. As a result of the contractile power of the normal uterine muscle, as well as of the pressure brought to bear upon the tumor by its continuous enlargement, it is forced along the line of least resistance, which must be toward the serous or mucous covering. A submucous myoma may become a *pedunculated polyp*, the length of the pedicle varying in different cases. Sometimes the pedicle may be sufficiently long for the polyp to project from the os uteri, or even from the vulva. Similarly formed subserous polypi occur. As a result of twisting or kinking of the pedicle the blood-supply to the polyp proper may be arrested, and extensive necrosis, or even gangrene, may occur. Wherever a myoma occurs it may be distinctly circumscribed, surrounded by fibrous capsule, or an ill-defined irregular mass in the midst of the muscle-tissue.

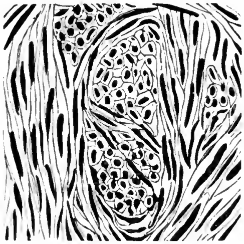


FIG. 190.—LEIOMYOMA.—(*Gould.*) The rod-shaped nuclei are shown in longitudinal section of the pseudo-bundles at the margin, and in transverse section in the center, of the illustration.

Microscopically, leiomyomata are made up of elongated spindle-cells, with rod-shaped nuclei, more or less distinctly grouped into fasciculi of various sizes; the connective tissue varies in quantity. The irregularly arranged muscle elements pass in all directions through the tumor. The few blood-vessels present are found in the connective tissue. Occasionally, leiomyomata are telangiectatic. Such richness in blood-vessels, however, is rare. More frequently a tumor contains comparatively large, irregular sinuses, which, in the larger tumors, may attain a transverse diameter of from 1 to 1.5 cm., and possess a tortuous

[1] Williams, "Lancet," Sept. 23, 1899.

length of from 5 to 10 cm. Such irregularly formed cavities may contain thrombi. (See p. 275.)

The most frequent secondary changes[1] affecting these tumors are calcareous infiltration (so-called "womb-stone") and fatty and myxomatous degenerations. Inflammation (due to injury), abscess formation, ulceration, and other necrotic processes occur. Clinically, the leiomyomata are benign tumors, but sarcomatous transformation is occasionally seen. There are on record a few cases of generalization of leiomyomata.[2]

Rhabdomyoma[3] is exceedingly rare, and is usually congenital. It is not improbable that tumors of this class are met with only as a result of the higher evolution of sarcomatous tissue (*myosarcoma*), in which the imperfectly developed muscle remains, for the most part, in an embryonic stage. The muscle-fibers present in rhabdomyoma are irregularly formed, and are often more or less spindle-shaped or club-shaped. As already stated, the tumor is in most instances congenital, and is usually found in the kidney, heart, or uterus.

VI. Angiomata are tumors formed of, or following, the type of vessels—either blood-vessels or lymph-vessels. The term angioma has been applied to tumors composed of blood-vessels, and has that significance when used alone. For the purpose of description it is purposed to divide the angiomata into hemangioma and lymphangioma.

(A) **Hemangiomata** are tumors consisting of blood-vessels bound together by a small amount of connective tissue. Some of these may be composed of newly formed blood-vessels, while others consist of more or less altered pre-existing vessels. The pure hemangiomata are composed of tissue entirely of new formation, but, by many, the tumors formed by alteration in pre-existing vessels are included under this name.

Simple Hemangioma (*Simple Nevus, Telangiectoma, Birth-mark, Mother's Mark, Angioma Telangiectoides*).—This is the most common variety, and affects the skin and subcutaneous tissues. Simple hemangiomata are flat, slightly elevated, sessile tumors of a violet or dark-red color, rarely bright red or pink; they are most frequently located upon the face, around the orbit, or on the neck, are usually congenital, and after birth may increase in size. On section, the vessels are found to be thin-walled (dilated, fusiform, cylindric, sacculated, or spheric), and embedded in a fibrous or cellulo-adipose matrix. There are usually two or more large vessels that establish a communication between the nevus and an adjacent artery or vein.

This form of angioma is most frequent on the skin of the face, scalp, neck, and back; they are sometimes seen in the labia, lips, tongue, and conjunctiva; rarely on the limbs. The varieties of simple hemangioma are: (*1*) *Nevus flammeus* (strawberry mark). These marks are of a bright-red color. (*2*) *Nevus vinosus*. These are of a dark-red or port-wine color, and are known as *port-wine marks*.

Cavernous Hemangioma.—This variety differs from simple hemangioma in that the vessels are less tubular. The tumor is composed of a series of irregular cavities formed by thin, fibrous septa. On

[1] McDonald, "Jour. Amer. Med. Assoc.," May 21, 1904, p. 1344.
[2] Devic and Galavardin, "Rev. de Chir.," Jan., 1904, p. 1.
[3] Capgrand, Thesè de Bordeaux, 1903.

section, these cavities appear as irregular sinuses separated by a nucleated fibrous network of spindle-cell tissue. Many of the walls are incomplete, which fact shows the communication between the spaces. The cavity walls are lined by endothelium. Cavernous hemangiomata are sometimes called *erectile tumors*, owing to their resemblance to erectile tissues, such as the corpus cavernosum of the penis. They are rarely congenital, and may develop from pre-existing simple hemangioma. Usually they occur early in life, and are rare in old age. When this form of tumor develops in the skin and forms a livid, raised, and uneven patch, it is referred to as a *nevus prominens*.

Angiomata are common in the skin and subcutaneous tissue, and occasionally are observed in the liver. They may occur in the kidney, spleen, uterus, intestines, bladder, voluntary muscle, bone, mamma, tongue, larynx, subperitoneal tissue—in fact, in almost any vascular tissue.

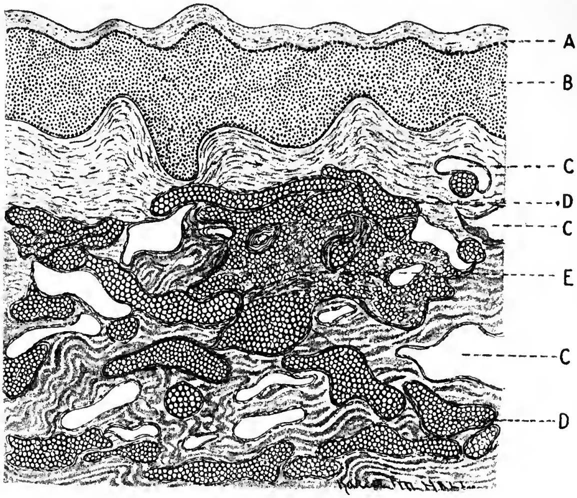


Fig. 191.—Cavernous Hemangioma from the Wall of Branchial Cyst.
A. Corneus stratum. B. Malpighian stratum. C, C, C. Caverns, the contained blood-cells of which have not been represented in the drawing; fourteen of these spaces are present. D, D. Caverns containing blood-cells. E. Area in which hemorrhage has occurred in hyaline matrix.

3. **Plexiform Hemangioma** (*Racemose Aneurysm, Aneurysm by Anastomosis, Cirsoid Aneurysm*).—Properly, this is not a neoplasm, but a pathologic alteration of the affected vessels. The vessels become dilated and convoluted, and, by pressure on the intervening tissue, cause atrophy. The vessel-walls are usually thickened. The tumor may be congenital or acquired. When occurring in the most superficial vessels, it is, by some, called a *nevus vasculosus*. Plexiform angioma sometimes follows injury. It usually involves the scalp (frontal and temporal region), extremities, labia pudendi, or spermatic cord.

(B) **Lymphangioma** is a tumor made up of dilated lymph-vessels. Rarely, the affected vessels may form distinct caverns or sacs—the

cavernous lymphangioma. The *lymphangioma cysticum* is a form of the cavernous type of the affection, characterized by the presence of large cysts, or a single cyst, usually situated in the neck or axilla, but sometimes found in the mediastinum or even the large viscera.[1] More commonly, the masses are of dilated vessels, and hence are analogous to the telangiectatic hemangioma already described. The altered structures are the lymph- and not blood-vessels.

Lymphangioma occurs most frequently in the tongue or lip, constituting *macroglossia* and *macrocheilia* respectively. In both these localities the morbid process is commonly associated with what appears to be a proliferative change in the unstriped muscle present. A special form of lymphangioma occurs in the lymphatics carrying chyle (chylous vessels, lacteals), and is called a *chylangioma;* when circumscribed and comprising a single cavity, the term *chylous cyst* is applied. In *lacteal* or *chylous varix* the affected vessels are tortuous, cylindric, or moniliform.[2] Lymphangioma is usually congenital, but may not be evident or begin to grow until some time after birth.

VII. Lymphoma, or tumor of the lymph-node, covers a multitude of conditions, many of which are in no sense tumors. Thus, the glandular enlargements of tubercle, syphilis, etc., are known as tuberculous or syphilitic lymphomata. To a related group belong the inflammatory lymphomata that accompany many infections: *e. g.*, chancroidal lymphoma, suppurative lymphomata of various kinds, and the enlargements affecting the cervical nodes in various throat affections, such as diphtheria and scarlet fever; none of these are tumors.

Lymphosarcoma is a sarcoma of the lymph-gland, and differs but little from other forms of sarcoma except in such histologic peculiarity as must arise from the site. The lymphatic enlargement that accompanies leukemia is probably an infectious process, with hypertrophy and hyperplasia of the cells and stroma of the lymph-nodes, or is a form of sarcoma attacking these structures; the latter view may be considered most popular at present. Such a condition is noted in Hodgkin's disease, when the hypertrophied glands are known as lymphadenomata. (See Diseases of the Lymph-glands, Part III.)

VIII. Myxoma.—This form of tumor is composed of mucous tissue, which is not, strictly speaking, an adult structure; it is, at least, the lowest grade of adult connective tissue. The tissue may be identical with that surrounding the vessels of the umbilical cord (Wharton's jelly), and resembles the vitreous humor. The tumor always contains a certain amount of fibrous stroma, and may resemble an edematous fibroma. In fetal life myxomatous tumors are met with in those subcutaneous tissues from which fatty tissue is later developed Macroscopically, the tissue appears as a homogeneous, structureless, gelatinous mass. The majority of the cells present are angular and stellate, with long anastomosing prolongations; others are indistinct (owing to the refractory nature of the intercellular substance), oval, spheric, or fusiform in shape. The blood-vessels are readily located, but are few in number. Frequently, between the cells fine elastic fibers can be demonstrated.

Clinically, myxoma is a peculiar, soft, gelatinous tumor, grayish or

[1] See Cystoma.
[2] See Elephantoid Diseases, p. 210

reddish-white in color, and on section yields a gelatinoid, whitish, albuminous, or mucilaginous material. Myxomata usually occur after middle life, are of moderately slow growth, may be single or multiple (commonly multiple), vary in size (rarely large), and not uncommonly recur after removal. This return may be due to imperfect removal, after which the remaining myxomatous elements grow with increased activity. Myxomata, when arising in the submucous or subcutaneous tissues may be pedunculated or sessile; rarely, the mass is lobulated. Primarily, they are benign tumors; occasionally such a tumor may become sarcomatous and the presence of myxomatous masses in sarcoma (myxosarcoma) is frequently observed. Hemorrhage (capillary), if extensive, may convert a large part of a myxoma into a blood cyst; fatty degeneration is sometimes present; they may become inflamed, ulcerated, or necrotic.

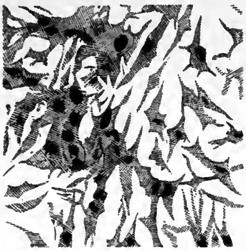


Fig. 192.—Myxoma.

Myxomata are restricted to the connective tissues, from any of which they may arise. They are most common in the subcutaneous and subserous fat, but also occur in the submucous (nares, uterus) and intermuscular tissues. In periosteum and medulla of bone, connective tissue of organs, and perineurium they are rare. Myxomata occasionally spring from the placenta.

Embryonic Connective-tissue Tumors.

Sarcoma.[1]

The sarcomata are tumors composed of embryonic connective tissue in which the cellular constituents usually predominate over the intercellular substance. The embryonic cells tend to infiltrate the surrounding tissues, as a result of which sarcomata are rarely, if ever, encapsulated. If a capsule surrounds the growth, it may have resulted from condensation of adjacent tissues, or it may be a part of the tumor; in either case it is sure to be infiltrated by the tumor cells. As a rule, the sarcomata contain very little fully formed fibrous tissue, the whole mass being composed of embryonic cells; the cells are uninucleated or multinucleated, and rarely possess a limiting membrane; the shape, size, and arrangement of the cells determine the variety of the tumor. The intercellular substance, which is usually small in amount, is closely connected with the cells, as in all connective tissues. The consistence of the tumor depends upon the character of the cell and intercellular substance, and upon the presence or absence of a fibrous stroma. The blood-vessels are very numerous, and are usually in direct contact with the cells, or they may be separated from them by a layer of thin fibrillated tissue. The vessels frequently lack distinct walls, and are marginated by the densely packed cells of the neoplasm. These cells may become detached, and may be carried along in the current; hence, *sarcoma spreads by the blood-vessels*. Owing to the thinness of the walls

[1] Borst, "Die Lehre v. d. Geschwulst. m. e. mikroscop. Atlas," Wiesbaden, 1902. A. and H. Malherbe, "Recherches sur le Sarcome," Paris, 1904.

of the blood-vessels, hemorrhage into the parenchyma of the tumor is often observed; the extravasated blood undergoes hemolysis, yields its contained coloring-matter, and pigments the matrix of the neoplasm. The quantity of blood may be large and form a cyst within the tumor. As will be seen later, true melanosis arises from other causes. As a rule, the periphery of the tumor is not clearly defined, there being no line of demarcation between the sarcoma and adjacent structures. When the tumor is of slow growth, an apparent capsule (pseudocapsule) may be formed by condensation of the contiguous connective tissues.

Clinical Characters.—As a rule, sarcomata develop most frequently in early and middle life, but may occur at any age, and are among the most malignant of tumors. They are characterized by their tendency to extend locally, to infiltrate surrounding structures, to recur after removal, and to give rise to metastasis. They may be localized,

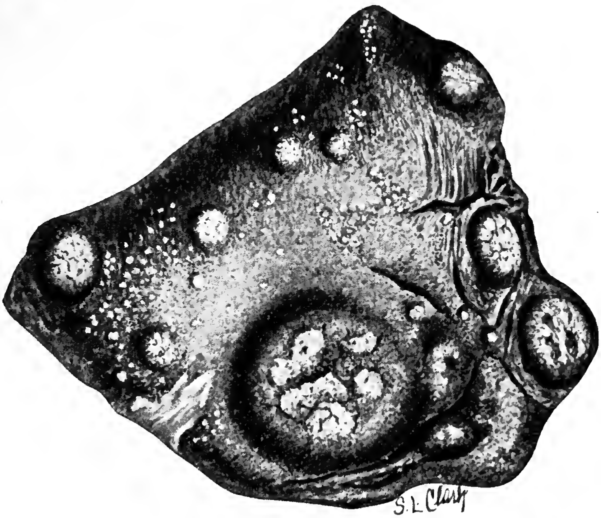


FIG. 193.—LUNG, PART OF SEROUS SURFACE: SECONDARY SARCOMA.
The larger distinctly elevated masses are the oldest; similar smaller nodules are more recent, while the youngest growths are shown as minute (miliary) grayish-white or white subserous dotlets. The specimen is a part only of the lower lobe; reproduction natural size. The incised surface of the same specimen is shown in Fig. 194.

and at first sharply circumscribed; but are liable to become rapidly disseminated, both by local infiltration and metastasis. Secondary growths occur most frequently in the lung. Sarcomata may disseminate much more rapidly than carcinomata. The round-cell and large spindle-cell varieties are of rapid growth and are very malignant. The small spindle-cell variety is much firmer, of slower growth, and less malignant. When subperiosteal, they are more malignant than when located in the center of the bone.

Sarcomata are prone to irregularity in growth, and often remain quiescent during long periods. This phenomenon is more commonly seen in primary tumors than in metastases or recurrent growths. Usually these periods of **latent malignancy** are brief, but occasionally during months or even years a tumor may cease to grow; rarely some reduction

in size takes place. Rolleston reports a case under the care of Whiting[1]—an osteosarcoma of the humerus—of fifty years' duration. It is possible that some of these neoplasms were nonmalignant tumors that eventually became sarcomatous. The size of the neoplasm bears absolutely no relation to its malignancy. I have seen a sarcoma so small that it was unobserved until it suddenly increased in size and gave rise to a rapidly fatal metastasis in the course of a few weeks. Wide-spread dissemination of these tumors (**sarcomatosis**) is due to the entrance of tumor cells into the circulation. Loeper and Louste[2] have shown that the sarcoma cells may occasionally be identified in the blood. For such demonstration 15 or 20 drops of blood should be allowed to flow directly into 15 c.c. of a 1 per cent. aqueous solution of acetic acid; the acid destroys the erythrocytes and, by centrifugalization, the leukocytes and tumor cells may be deposited. A drop of the sediment is spread on cover-glasses or a slide, fixed and stained in the same manner as blood.[3] When the cells of the neoplasm are small and round, it may be difficult to differentiate them from mononuclear leukocytes. The attempt, however, is sometimes successful and constitutes an important diagnostic and prognostic sign.

The following are the chief signs of malignancy in any tumor, be it sarcoma or carcinoma. They are inserted here by reason of their special applicability to the sarcomata:

1. *Size of the Cell.*—As a rule, it may be said that the smaller the cells of a tumor, the more malignant will it probably be. Thus, the small round-cell sarcoma is a more malignant tumor than that composed of giant-cells, and the small epithelial cells of a scirrhous cancer of the mamma give rise to a more malignant growth than the large, flat epithelial cells of the skin, as seen in the squamous epithelioma.

2. *The Number of the Cells.*—If a tumor be purely cellular, the likelihood of its recurrence is great.

3. *Activity of the Cells.*—One of the chief diagnostic features of a malignant tumor is the tendency of its nuclei and cells to divide; if on section a large number of the cells show some stage of mitosis the prognosis is unfavorable; such tumors practically always manifest rapid local extension, and prompt recurrence.

4. *Shape of the Cell.*—A small, round cell, like a lymph corpuscle will be more readily transported by a blood-vessel or lymphatic than one that is long and tapering; hence the former will have a greater tendency than the latter to reproduce the tumor in neighboring parts. The round-cell sarcoma forms secondary tumors in neighboring organs, infiltrates blood-vessels, and evinces metastasis with greater readiness than one of the spindle-cell type. The foregoing applies not only to local infiltration, but also to distal metastases. The large, irregular cells of the squamous epithelioma will be less likely to reach distant parts through the blood-vessels or lymph-vessels than the small, round, plastic cells of a sarcoma.

5. *The Manner in Which the Cells are Held Together.*—So far as regards the sarcomata, at least, the more loosely the cells are held together, the greater is the tendency of the tumor to recur. This is

[1] "Brit. Med. Jour.," Jan. 7, 1905, p. 19.
[2] "C. R. Soc. de Biol.," 1904, lvi, p. 153.
[3] See technic of Blood Examination, Part III, Chapter I.

equivalent to saying that the more fluid the intercellular substance, the more malignant the tumor. Fluidity of the intercellular substance implies that the neoplastic cells are loosely bound together; this lack of cohesion between the elements of the tumor permits of the ready dislodgement of one or more cells, or masses of cells, and hence favors displacement of the tumor elements into the lymphatics and blood-vessels. The fluidity of the intercellular substance may be partly judged by the consistency of the tumor; a soft, almost fluctuating tumor, possesses but little firmness in the intercellular substance. Such soft, pseudofluctuating tumors are not infrequent among the sarcomata. The author has known of one or more instances in which the surgeon has cut into a sarcoma under the impression that he was dealing with a cyst or a cold abscess. Indeed, the cellular elements of some of the

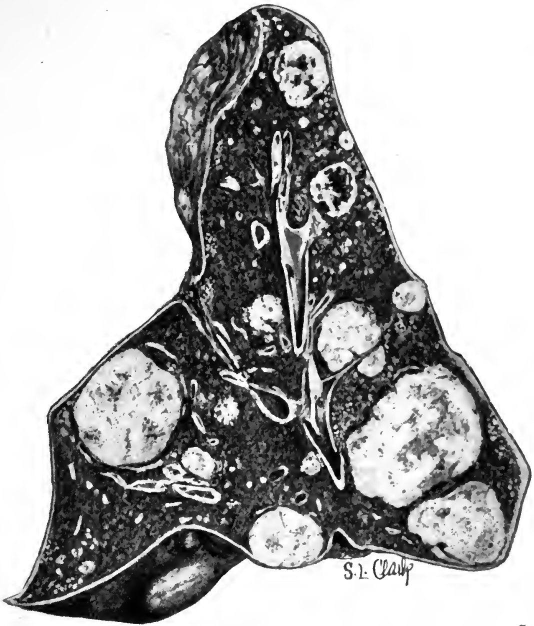


FIG 194.—LUNG, INCISED SURFACE OF PART OF ONE LOBE, SECONDARY SARCOMA. The serous surface is shown in Fig. 193. (Natural size.)

small, round-cell sarcomata are so loosely attached that a needle—for example, an exploring needle—passed into the tumor may not infrequently be moved about from place to place, the operator not being able to detect the presence of any solid constituent within the mass.

6. *Absence of Any Tendency to Complete Their Development.*—Of all signs of malignancy, this, in the case of sarcoma, is perhaps the most unequivocal. The cells do not complete the formation of connective tissue that normally they were destined to generate. Instead of their energy being occupied in the metabolism necessary to secrete the matrix peculiar to each, it is wholly expended in the process of reproduction. At certain stages in the process of repair the proliferated cellular elements may constitute a mass of embryonic tissue

which, if we take into consideration only the character of the cells, can not be differentiated from sarcomata possessing similar cellular elements. In the tissue elaborated during reparative processes we nearly always see the cellular elements, in one or more parts, progressing to their proper histologic end—cicatricial tissue, osseous tissue, etc. In some sarcomata an effort in this direction may be apparent. It is, however, never fully successful; if it were the tumor would not be a sarcoma.

7. *Tendency of the Cells to Spread into Neighboring Interfibrillar Spaces.*—In examining a tumor, the tissues round about it should be carefully investigated, with a view to determining whether the cells of the tumor have invaded adjacent structures. If so, such a tumor is dangerous, and should be excised with a wide margin. A single cell left in the surrounding tissue may reproduce the tumor. Cancer of the mamma shows more tendency to penetrate the surrounding stroma of the gland than perhaps any other tumor. It is also one of the most malignant neoplasms.

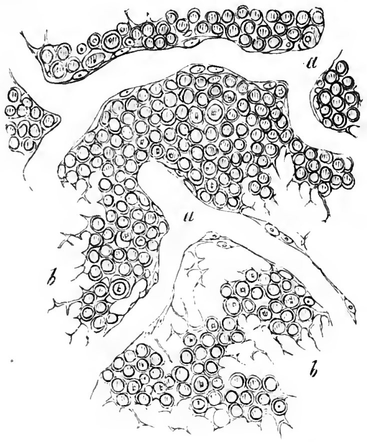


FIG. 195.—ROUND-CELL SARCOMA.—(*Rindfleisch.*) × 300 diameters.
a, *a*. Blood-vessels without distinctly formed walls. *b*, *b*. Points where the round cells have partly fallen out, showing the slight basis of reticular tissue.

Varieties of Sarcoma.—The subdivision of sarcoma into small groups is usually based on the size and shape of the cells or the presence of more fully formed connective tissue so arranged as to give rise to alveoli. The foregoing bases for subdivision render it possible to recognize (1) round-cell sarcoma, the cells of which may be small or large; (2) spindle-cell sarcoma, which also may be of the small-cell or large-cell variety; (3) giant-cell sarcoma; (4) mixed-cell sarcoma; (5) alveolar sarcoma. To these must be added certain neoplasms in which special characters demand some additional appellation. When the tumor cells elaborate pigment, the neoplasm is called a melanotic sarcoma. The term osteosarcoma has been applied to tumors occurring in bone, and also to those in which osseous or osteoid tissue is produced; most sarcomata of bone contain bone-like structures, and hence may properly be called osteosarcomata; the term, however, should be applied for the purpose of indicating the presence of such tissue in the neoplasm and without special regard to the particular structure from which the tumor arose. In many of the sarcomata the cells are pleomorphous, and it is often difficult to state definitely where a given tumor should be grouped; it is customary to classify a neoplasm according to the dominant cell present. Most sarcomata contain more than one type of cell, and hence would, with propriety, be designated mixed-cell sarcoma. In the giant-cell sarcoma most of the cells are not of unusual size, but the presence of characteristic, large, polynuclear elements usually justifies the name given.

1. **Round-cell Sarcoma** (*Encephaloid* or *Medullary Sarcoma*) is a rather infrequent form of sarcoma, and consists of round cells with very little intercellular substance. The cells contain large, easily stained nuclei. Blood-vessels are abundant, and appear as channels or sluiceways passing directly between the cells; usually lymphatics cannot be demonstrated. The cells rapidly infiltrate the surrounding tissues; the tumor tends to recur after removal, and gives rise to secondary deposits. The variety known as *large round-cell sarcoma* differs from the

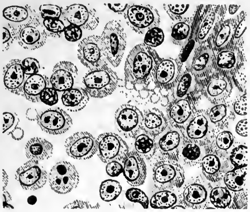


FIG. 196.—ROUND-CELL SARCOMA.—(*Gould.*)

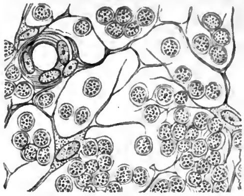


FIG. 197.—ROUND-CELL SARCOMA OF A LYMPH-NODE.—(*Gould.*)
The cells have dropped out at places, showing the remainder of the intercellular trabeculæ.

small round-cell variety in that the cells are larger and more irregular in size; they are usually mononuclear, although a few polynuclear elements may occasionally be found; such cells rarely contain more than two nuclei and often it is possible to recognize that these have resulted from imperfect division. The round-cell sarcoma may occur in any tissue and at any age, even in the fetus *in utero*. It is a soft, often fluctuating, rapidly growing tumor, which, when on the surface, ulcerates early, and usually proves fatal in a few months.

2. **Spindle-cell Sarcoma** (*Recurrent Fibroid* (Paget); *Fibroplastic Tumor* (Lebert); *Fibrosarcoma; Oat-cell Sarcoma; Fasciculated Sarcoma*).—Tumors containing spindle cells are the most common of the sarcomata. They are firm in texture, and on section are translucent, and grayish or yellowish-white in color. As a rule, the spindle-cell sarcomata grow much less rapidly than the round-cell variety. They are divided into (*a*) small-cell and (*b*) large-cell varieties.

FIG. 198.—SPINDLE-CELL SARCOMA.—(*Gould.*)

(*a*) **Small Spindle-cell Sarcoma.**—This variety resembles somewhat the fibromata; the cells are fusiform in shape, with oval nuclei; the intercellular substance, of which there is very little, may be fibrillated. The cells and intercellular substance are rarely arranged in bundles, but usually pass in every direction. Except that it is firmer, grows with less speed, and does not so quickly ulcerate or prove fatal, the tumor clinically resembles the round-cell sarcoma. Round-cell sarcomata are usually round or oval; the spindle-cell forms of the tumor are frequently bossed or tuberous; this latter character is due to multicentric nodules that have developed around, or contiguous to, the primary mass.

Spindle-cell sarcomata are most common in the periosteum, fasciæ, eye, antrum, breast, and testicle, but may occur in any connective tissue. These tumors tend rapidly to infiltrate the surrounding tissue and to recur locally after removal.

(*b*) **Large Spindle-cell Sarcoma.**—This differs from the small spindle-cell variety in that the cells are larger, with prominent nuclei and nucleoli, which are frequently multiple; there is very little intercellular substance, with slight or, it may be, no fibrillation. The tumor is likely to be very soft, and is sometimes stained by extravasated blood; the growth is rapid and the neoplasm very malignant. These tumors frequently become osseous (osteosarcoma or osteoid sarcoma), especially when occurring in the periosteum or bone.

FIG. 199.—SARCOMA OF THE MAMMARY GLAND; TUMOR OF SEVERAL YEARS' DURATION; PATIENT THIRTY-FIVE YEARS OF AGE.

A. Nipple that appears slightly retracted; this appearance is not due to a pulling-in of the nipple, as in carcinoma, but results from the forward projection of the skin caused by the enlarging neoplasm. *B*. One of the many secondary bosses over which the skin is thin and shining. These nodules result from the polycentric local dissemination.

3. **Giant-cell Sarcoma** (*Myeloid Sarcoma*).—This variety resembles the spindle-cell growths, and usually occurs in connection with bone. Such tumors contain many large polynucleated cells (see Fig. 201), and fusiform cells like those of the spindle-cell varieties; indeed, giant-cell sarcomata are practically all mixed-cell tumors in which the giant-cells constitute more or less conspicuous elements. In addition to the polymorphism of the cells, such tumors not uncommonly manifest a tendency toward an alveolar arrangement. In properly stained specimens the giant-cells are sometimes sufficiently large to be easily recognized by the unaided eye. In very rare instances the giant-cell sarco-

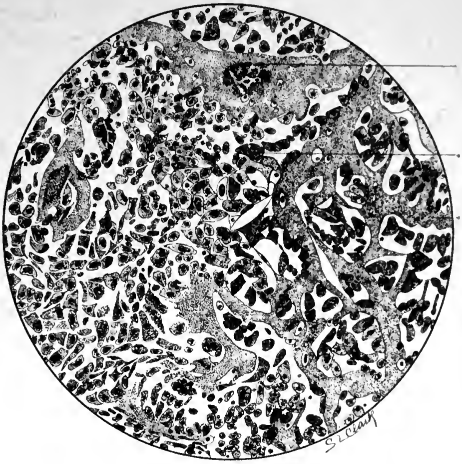


FIG. 200.—SARCOMA, MIXED-CELL, WITH CALCIFICATION OF PART OF THE INTERCELLULAR MATRIX; OSTEOSARCOMA.

A. Calcified area in osteoid matrix. *B*. Osteoid tissue which, in some areas, gives rise to an alveolar arrangement *C*. Osteoblastic cell.

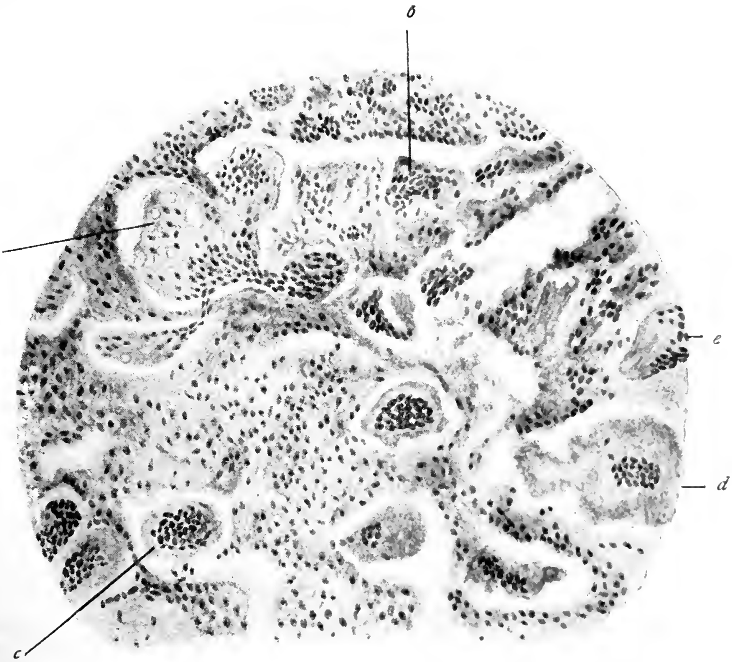


FIG. 201.—GIANT-CELL SARCOMA.—(*Specimen lent the author by Dr. Rosenberger.*)

a b. c, d, e. Giant-cells. The large giant-cell *a* shows vacuolation and dissemination of the nuclei, with pseudopod-like extension suggestive of ameboid movement. This condition is not commonly observed. The cell contains over one hundred nuclei. The giant-cell *c* is more nearly typical. The admixture of other cellular elements—the usual condition noted—is well shown. (½-inch objective, 1-inch ocular.)

mata contain a small quantity of pigment. The large giant-cells are arranged in almost direct contact with the other cellular elements, there being very little intercellular substance. As a rule, the blood-vessels are not plentiful, but the tumors may be exceedingly vascular and sometimes pulsate; they frequently become cystic. They are usually firm. Giant-cell sarcomata are rare after middle life, and are the least malignant form of the sarcoma; they usually spring from the periosteum or endosteum. When they originate in the upper or lower alveolar process, they constitute one variety of the *epulis*.

4. **Mixed-cell Sarcoma.**—This variety contains round cells (large and small) and spindle cells (large and small), and otherwise resembles the round-cell and spindle-cell varieties. A sarcoma in which all the cells have practically the same size and shape is rarely seen; even when the cells of one area in the tumor are approximately all alike, examination of other areas will usually disclose cellular elements that are quite dissimilar. To this extent it may be said that nearly all sarcomata are mixed-cell tumors. As the malignancy, consistency, and, to a certain extent, the other characteristics of a sarcoma depend upon the size and shape of the cells, it will at once become apparent that a tumor largely composed of a certain cell will be most likely to possess the attributes with which that particular cell is commonly endowed. For this reason it is customary to speak of a sarcoma as spindle-cell sarcoma, even though it contains a minimum of cells possessing other shapes. The exception to this rule is in giant-cell sarcoma, where the giant-cells are not abundant as compared with the other cellular elements.

FIG. 202.—ALVEOLAR SARCOMA.—(*Gould.*)
Compare with glandular carcinoma, figures 206 and 207.

5. **Alveolar Sarcoma.**—In this the fibrous stroma resembles that of cancer. The nests of cells are separated by thin fibrous bands. The cells are sharply distinguished from the fibrous network, and are loosely adherent. The blood-vessels follow the course of the fibrous tissue and rarely, if ever, enter the cell groups. In handling the sections, should the nest of cells drop out, the remaining fibrous stroma closely resembles transverse sections of air vesicles (alveoli). Under the microscope there is no other variety of sarcoma so likely to be mistaken for carcinoma. A little experience will usually enable one to avoid this error, particularly if the blood-vessels in the stroma be carefully studied. In the sarcoma many of the vessels are without walls; in the carcinomatous stroma the walls of the vessels will, in most cases, be normal, or may even be thicker than usual. Alveolar sarcomata are not uncommonly melanotic. (See Fig. 204.)

Melanotic Sarcoma (*Melanosarcoma*).—Pigmentation may occur in any variety of sarcoma, and is frequently due to hemorrhage, followed by alteration in the hemoglobin and pigmentation. In certain forms of sarcoma the abundance of pigment can not be fully accounted for by presuming an antecedent hemorrhage; the tumor cells seem able to elaborate pigment. These tumors may be brown or slate-colored, and in some instances are almost black. (See Fig. 203.) Sections

show the pigment in and between the cells. The coloring-matter, contained in neoplasms of this type, is produced by special cells called *melanoblasts*. The tumors are very malignant. Occasionally, the

FIG. 203.—MELANOTIC SARCOMA SPRINGING FROM THE SUBCUTANEOUS OR POSSIBLY FROM THE PERIOSTEAL CONNECTIVE TISSUES.

The intensely dark slate color, almost black, is well shown. The infiltrating margins of the growth could be approximately outlined by the unaided eye on account of the intensity of the pigmentation. The submaxillary lymphatics were enlarged and were crowded by pigment cells. Histologically, the pigment was within and between the cells. and was scattered through the tumor at all points.

amount of pigment produced is sufficient notably to influence the skin, the mucous membranes, and sometimes the urine; the pigmentation of the skin may be intense, giving rise to a discoloration resembling that seen in Addison's disease.

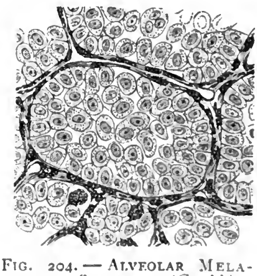


FIG. 204.—ALVEOLAR MELANOTIC SARCOMA.—(*Gould*.)

Important among the melanomata are certain tumors, frequently arising from pigmented moles, about the exact nature of which opinions are divided. Prior to 1891 all agreed that these neoplasms were sarcomatous; in that year Eve suggested that they might be carcinomata, and in 1892 Unna, independently, urged their cancerous nature. Pathologists usually believe them sarcomatous, and, following Unna, dermatologists regard them as carcinomatous; owing to the wide distribution of the neoplasms the condition is called **sarcomatosis** or **carcinomatosis cutis.** The primary mole from which the neoplasm arises may show little or no enlargement and rarely attains a diameter of 1 cm. or 2 cm. The amount of pigment in the primary and secondary growths varies from a slight, scarcely demonstrable

quantity to such an abundance that the neoplasms are almost black, the skin irregularly mottled, and the coloring-matter excreted in the urine. In the tumors the pigment appears to be melanin and in the urine colorless melanogen, which, by oxidation—exposure to the air or treatment with chemic oxidizers—becomes perceptible; occasionally a true melanuria may be present. The tumors are exceedingly malignant, the patients rarely surviving more than one or two years.[1]

Endothelioma (*Plexiform Angiosarcoma*).—In this variety of neoplasm the cell nests are formed by proliferation of endothelial cells. The tumor is highly vascular, due either to pre-existing or to newly formed vessels, the walls of which become thicker, until at length the intervascular spaces are entirely filled. Endotheliomata occur in the arachnoid

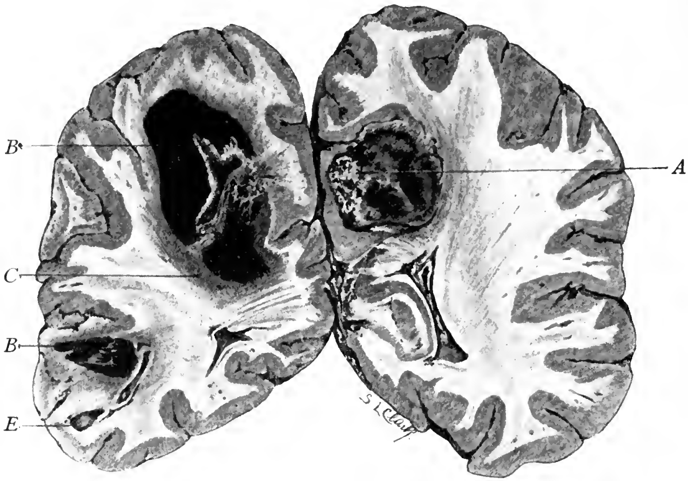


FIG. 205.—CEREBRUM. CORONAL SECTION, ANTERIOR ASPECT; SUPERIOR PARIETAL LOBULE AND POSTERIOR PART OF TEMPORAL LOBE. (THREE-FIFTHS NATURAL SIZE.)—(*Jefferson Medical College Hospital Laboratories, No.* 2538.)

Melanotic sarcoma, secondary to primary growth in pigmented mole of skin of back. *A*. Secondary nodule, showing considerable hemorrhage in the interior of the new growth and a scanty, irregularly distributed, but narrow band of peripheral hemorrhage. *B*. Similar mass in opposite hemisphere. The hemorrhage in this area is around the growth, which is considerably compressed. *C*. Blood-stained zone surrounding mass; it will be observed that the peripheral blood tinging of the white matter is more marked on this side than the other, due to the more abundant hemorrhage and its peripheral distribution. *D* and *E*. are also areas of hemorrhage containing varying quantities of neoplastic tissue; the latter which, in the absence of extravasated blood is grayish-brown or nearly black, is further obscured by hemoglobin imbibition.

and pia mater, and usually on serous surfaces, but have been observed in the viscera, bone, mamma, and subcutaneous tissues; the parotid neoplasm known as a "mixed tumor" is often, if not always, an endothelioma. Occasionally, when occurring in the pia mater, the proliferated endothelial cells are aggregated into small, spheric nodules of a peculiar, shiny, lustrous, pearly appearance; the tumor is then referred to as a *cholesteatoma*. Endotheliomata not uncommonly assume a distinctly alveolar type. The large, flat, endothelial cells springing from the serous surface, and occurring within distinct alveoli formed of connective tissue,

[1] The literature of the subject may be traced from the following: Eve, "Practitioner," Feb., 1903, p. 165. Wilson and Kalteyer, "Amer. Jour. of Med. Sci.," Nov., 1903, p. 751.

afford a picture so closely resembling carcinomata that accurate differentiation seems at times impossible. This close resemblance has led to an unfortunate complication of names, such tumors being sometimes called *endothelial carcinomata*, and, again, *epitheliomata* of the serous membranes. Usually, a careful examination of a large number of sections will disclose areas distinctly sarcomatous. The shape, arrangement, and character of the cells, associated with the poor development of the blood-vessels, point conclusively to the diagnosis of sarcoma. The author has recently had an opportunity to examine such a tumor springing from the tonsil or pharyngeal wall. The examination of many sections has led the writer to believe that it is not impossible that some of these tumors may represent combined or associated processes; the coincidence of sarcoma and carcinoma in the same individual, or even in the same organ, occasionally occurs; the author has seen giant-cell sarcoma and scirrhus together in the female mamma. Tumors of endothelial origin arising from the cells in the lymph-spaces are called

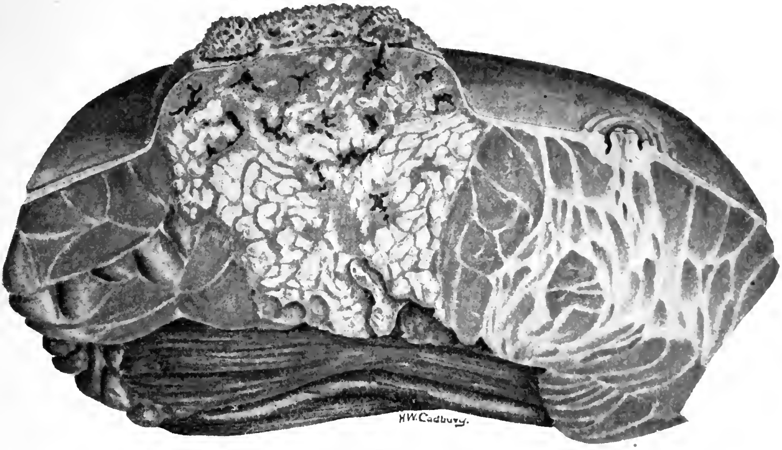


FIG. 206.—MAMMA, LYMPHANGIO-ENDOTHELIOMA.
Removed by Prof. J. Chalmers DaCosta. Section of this tumor is shown in Fig. 207.

lymphangio-endotheliomata; those developing from the endothelium of the blood-vessels, **hemangio-endotheliomata.** Apparently some of these neoplasms arise from the perivascular endothelium, and to these has been given the name **perithelioma.** With regard to the malignancy of the endothelioma, it may be stated that, as a rule, they grow slowly, manifest metastasis late, if at all, and evince little tendency to recur if thoroughly removed. The high mortality from endothelioma is due to inaccessibility of the tissues ordinarily involved.[1]

Psammoma (*Angiolithic Sarcoma*) is a peculiar tumor, containing sand-like masses and originating in the brain and its membranes, more

[1] The important literature bearing on endothelioma may be found in, or traced from, references given in the following articles: Bonheim, "Münch. med. Woch.," April 26, 1904, p. 741. Keen, "Jour. Amer. Med. Assoc.," April 30, 1904. Funke, "Amer. Med.," July 16, 1904, p. 109. Gilford and Davis, "Practitioner," Dec., 1904, p. 729. Kirchner, "Deut. militar. Zeit.," 1905, H. 1. Johnson and Lawrence "Trans. Path. Soc. of London," 1903, vol. 54, p. 329.

particularly in the pineal gland and the choroid plexus; it contains fine, chalky, or calcareous concretions showing concentric lamination. Colloid or hyaline change may occur in or near the concretions; indeed, if the lime salts be cautiously dissolved by acids, a concentrically arranged hyaline matrix commonly remains. The occurrence of similar calcific deposits in tumors, the tissues of which approach the adult type, shows that the presence of calcareous deposit is not restricted to sarcoma, but may be seen in other growths developing in the areas indicated.

Chloroma[1] is another oddly formed cellular tumor; a section of the gross specimen presents a light green or dirty brown color, which soon fades on exposure to air. Its cause is not known; it occurs chiefly in the

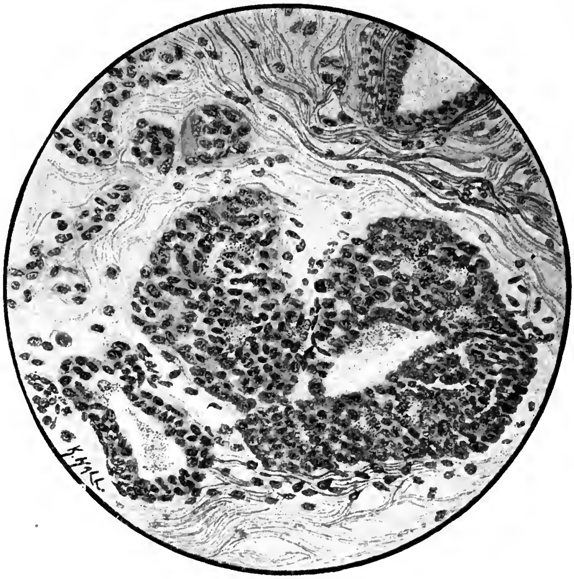


FIG. 207.—MAMMA, LYMPHANGIO-ENDOTHELIOMA.
In the upper right quadrant is the margin of a mammary duct. Section of mamma shown in Fig. 206.

periosteum of the skull, but may involve the subcutaneous tissues, muscles, viscera, and lymph-nodes (chlorolymphoma). The blood frequently shows a mononuclear leukocytosis resembling that of lymphatic leukemia. Histologically the tumor is composed of a scanty reticulum and cells, the latter resembling the large lymphocytes of the blood; occasionally granules are found both within and between the cells. Some cases are accompanied by the hemorrhagic diathesis.

Cylindroma is produced by partial hyaline or mucoid degeneration of a sarcoma, or when there is a combination of sarcomatous and myxomatous tissue. The term is also applied to a variety of tumor of the epithelial type, known as *cylindroma carcinomatodes*, which is character-

[1] See Dock and Warthin, "Trans. of Assoc. of Amer. Physicians," 1904.

ized by the formation of peculiar homogeneous spherules within the cell nests; it is probably a colloid degeneration.

Sarcomata are particularly liable to secondary change. Areas in the tumor may show a decided disposition to complete the developmental tendency of connective tissue. As a result of such processes true bone formation may occur—*osteosarcoma;* or cartilage may be produced—*chondrifying* or *chondroid sarcoma*, or *chondrosarcoma.* Lipomatous sarcomata are rare. Sarcomata containing more or less mucoid tissue (*myxosarcoma*) are more frequent. In such tumors the change may be conspicuous in the intercellular substance, or it may be evident within the cells themselves. Conversion of the tumor cells into a structure resembling adult fibrous tissue has already been referred

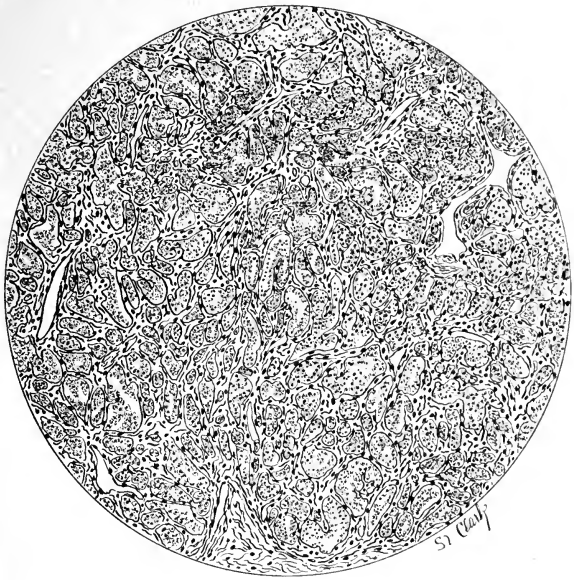


FIG. 208.—PERITHELIOMA OF THE CAROTID BODY.
Leitz 24 mm., Oc. A. Reduced one-half.

to in considering fibrosarcoma. Of the infiltrations to which sarcomata are liable, calcification is the most common. Such tumors, containing calcific collections or concretions, are sometimes called *osteoid sarcomata*, a name which is particularly objectionable as it resembles so closely *osteosarcoma*, a term applied with an entirely different meaning. Fatty degeneration of sarcoma cells occasionally occurs. Sometimes the distinctly fatty areas are conspicuous, and may be easily recognized as more or less irregular, yellowish patches. Cyst formation in the interior of sarcomata is occasionally observed; it is, however, a comparatively infrequent change.

As a result of the faulty development of the blood-vessel walls, areas of interstitial hemorrhage are not infrequent. These may assume

the character of a suffusion, the blood infiltrating between the tumor cells; more or less circumscribed areas of hemorrhage may also occur. When infection, ulceration, or superficial necrosis has removed the overlying skin or mucous membrane, sarcomata not uncommonly bleed, even profusely. With the lessened pressure resulting from destruc-

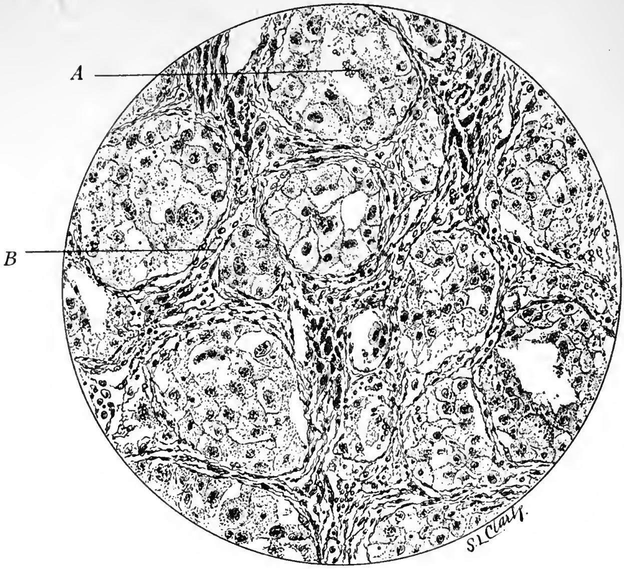


FIG. 209.—PERITHELIOMA OF CAROTID BODY.
Obj. B. and L. $\frac{1}{8}$-inch, oc. 1 inch. Reduced one-half. *A*. Red blood-cells in an alveolus. *B*. Blood-vessel in the stroma between alveoli.

tion of the overlying skin or mucous membrane the neoplasm may protrude as a fungoid growth, more or less narrowed at its base, and constituting a form of the *fungus hematodes* of the older writers. Infectious changes in the sarcomata may be evident. Extensive necrosis of the cells resulting from infection, and even gangrene of a large portion of the tumor, may occur. Such ulcerating surfaces may suffer saprophytic infection, and give off a penetrating, fetid odor. The patient's health may be profoundly influenced by the occurrence of infection; sapremia, true septicemia, or even pyemia sometimes develops.

DIAGNOSTIC FEATURES OF SARCOMA AND CARCINOMA.[1]

	Sarcoma.	**Carcinoma.**
1. Origin.	Entirely mesoblastic. (Connective-tissue type.)	Epiblastic and hypoblastic. (Epithelial-tissue type.)
2. Stroma.	Intercellular. Rarely forms alveoli.	Vascular connective tissue, which surrounds and forms the walls of the alveoli; these communicate with one another, and contain masses of epithelial cells.

[1] After Woodhead; modified and extended.

	Sarcoma.	Carcinoma.
3. Cells.	Granulation tissue or embryonic connective-tissue cells; shape and size vary.	Epithelial cells contained within alveoli; shape and size vary.
4. Intercellular substance.	May be present.	Absent, or merely fluid.
5. Vessels.	Embryonic in character. They are in direct contact with, or may be formed by, the special cells, slightly modified, of which the tumor is composed.	Well developed; entirely contained within the connective-tissue stroma, and supported by the walls of the alveoli. Seldom in contact with the cells.
6. Spreads.	*Primarily* and *secondarily* by blood-vessels, rarely by the lymphatics.	*Primarily* by lymphatics, except in the later stages, when it may also spread by blood-vessels, in which case it spreads with very great rapidity. *Secondarily* by blood-vessels.
7. Secondary changes.	Chondroid, osseous, calcific, and pigmentary changes frequent.	Very rare.
8. Growth.	Not invariably continuous. Likely to be interrupted.	Rapid. Continuous.
9. Site.	Primarily in deep structures; always from connective tissue.	Primarily in superficial structures or glands; always from epithelium.
10. Heredity.	Seldom hereditary.	May be hereditary.
11. Capsule.	Primarily, pseudoencapsulated; later, infiltrates the surrounding tissue.	Never encapsulated.
12. Fat.	Rarely, if ever, contains fat.	Nearly always contains fat.
13. Age.	Occurs most frequently before middle life.	Most frequent after middle life.
14. Injury.	Not uncommonly follows injury, such as trauma.	Rarely, a history of trauma, but may follow prolonged irritation. Especially is this true of the superficial forms.

MIXED TUMORS

Tumors Composed of Both Types of Tissue.

Teratoma.[1]—This rare variety of tumor is composed of epithelial and connective-tissue types (adult and embryonic), and originates in rudiments derived from the three layers of the blastoderm (ectoderm, mesoderm, and endoderm). Teratomata are congenital tumors, usually occurring in the sacral region (coccygeal tumors), the head and neck, mediastinum, or the abdominal cavity; they are common in the ovary, less frequent in the testicle, and occasionally are observed in the kidney and other viscera, and in the mediastinum.

They may be due to inclusion and imperfect development of one fetus within another, or to abnormal proliferative changes in the tissues of one fetus. They vary in size—may be small at birth, and may

[1] The most important literature on the subject can be found in, or traced from, the following articles: Steinert, "Virchow's Arch.," Nov. 4, 1903. Schlagenhaufer, "Wien. klin. Woch.," 1902, p. 571. Tédenat, "Revue de Chir.," Nov. 10, 1903, p. 514. Chiari, "Centralbl. f. allg. Path. u. path. Anat.," Dec. 31, 1904, p. 987. Henderson, "Jour. Amer. Med. Assoc.," July 25, 1903, p. 260. Joseph, "Deut. med. Woch.," 1903, No. 35. Féré, "Soc. de Biologie," March 14, 1903. See also references given under Dermoid Cysts.

remain stationary or continue to develop. As evidence of fetal inclusion, the tumor mass may contain structures definitely suggestive of organs. Teratomata are frequently cystic; they sometimes recur after what was believed to have been complete removal; such recurring tumors are thought by some to possess a sarcomatous element. Dermoid cysts are, by some writers, classed with the teratomata.[1]

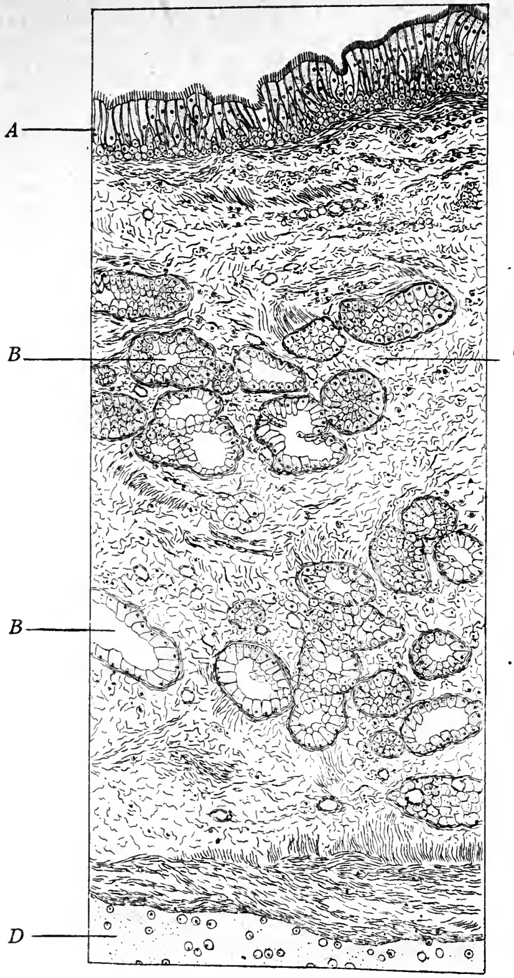


FIG. 210.—TERATOMA.
Section of cyst wall, case of teratoma of the sacrum, operated upon by Prof. W. W. Keen. Note the resemblance to the wall of a bronchus. *A*. Cylindric ciliated epithelium. *B*, *B*. Glands lined by low columnar epithelium. *C*. Blood-vessel. *D*. Cartilage.

Chorioepithelioma[2] (*Deciduoma malignum*, *Syncytioma*, *Sarcoma deciduo-cellulare*, *malignant placental polyp*, etc.) is a peculiar tumor the exact oncologic position of which has not been determined to the satisfaction of all observers. It has been regarded as a sarcoma and strongly resembles tumors of that group. Most authorities recognize the impossibility of definitely assigning the neoplasm to any recognized class, and some hold that a number of tumors are at present included under the one name and really constitute a group. The primary neoplasm is practically always in the uterus and usually follows labor or abortion. The tumor gives rise to extensive metastases by the blood; secondary growths are particularly prone to involve the lungs, brain, and kidneys. The primary and metastatic masses are exceedingly vascular and composed of large blood-sinuses containing structures resembling the chorionic villi, and

[1] See Dermoid Cysts.
[2] The important literature on the subject is quoted by Bland, "Jour. Amer. Med. Assoc.," June 10, 1905, p. 1827; bibliography.

FIG. 211.—TERATOMA OF TESTICLE.

Matrix composed of myxomatous and collagenous tissues; also containing smooth-muscle bundles and on the extreme left an island of fetal cartilage. The cysts are lined by columnar epithelium which in places is ciliated.

FIG. 212.—SYNCYTIOMA.

Case of Dr. Montgomery's, studied by Dr. Bland, in the writer's laboratory. Microscopic section of tumor removed from its central portion. *A, A, A.* Large wandering decidual cells. *B.* Leukocytes. *C.* Chorionic villi showing marked disturbance in Langerhans' cells. *D.* Non-nucleated protoplasmic mass.

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particularly characteristic are the large multinucleated protoplasmic masses similar to the syncytial cells. (See Fig. 212.) Chorioepitheliomata vary widely in malignancy; some growths prove fatal in a few weeks, while, in other cases, partial removal is followed by complete recovery. In the case reported by Noble it was recognized at operation that definite neoplastic tissue was left behind; the patient, however, recovered. Some writers speak of chorioepithelioma malignum and chorioepithelioma benignum as distinct neoplasms

TUMORS.

(Those printed in *italics* are malignant.)

- TUMORS.
  - Neoplasms
    - Epithelial (Epiblast and Hypoblast)
      - Adult (Typical Benign)
        - Papilloma
          - Skin warts.
          - Villous warts.
          - Intracystic warts.
        - Adenoma
          - Acinous.
          - Tubular.
        - Neuroma[1]
          - Ganglionic neuroma.
          - Myelinic neuroma.
          - Amyelinic neuroma.
        - Glioma
      - *Embryonic* (Atypical, Malignant)
        - *Carcinoma, or Cancer*
          - *Epithelioma*
            - *Squamous.*
            - *Tubulated.*
            - *Cylindric.*
          - *Glandular*
            - *Scirrhus.*
            - *Encephaloid.*
            - (*Colloid Mucoid; Melanotic.*)
    - Connective tissue (Mesoblast)
      - Adult (Typical or Benign)
        - Lipoma
          - Simple.
          - Fibrous.
        - Chondroma
        - Osteoma
          - Eburnated.
          - Compact.
          - Spongy.
        - Fibroma
          - Simple
            - Hard.
            - Soft.
          - Fibroma Molluscum.
          - Keloid.
        - Myoma
          - Leiomyoma (Unstriped).
          - Rhabdomyoma (Striped)
        - Angioma
          - Hemangioma (Blood-vessels)
            - Simple.
            - Cavernous
            - Plexiform.
          - Lymphangioma (Lymph-vessels).
        - Lymphoma (?).
        - Myxoma.
      - *Embryonic* (Atypical, Malignant)
        - *Sarcoma*
          - *Round-cell*
            - *Large.*
            - *Small.*
          - *Spindle-cell*
            - *Large.*
            - *Small.*
          - *Myeloid.*
          - *Mixed-cell.*
          - *Alveolar* (*Melanotic, Cystic, etc.*).
    - Mixed, (Both Epithelial and Connective-tissue.) .... Teratoma.
  - Cysts
    - (1) Retention (occluded excretory ducts).
    - (2) Exudation (accumulations in closed cavities).
    - (3) Cystomata (new formation).
    - (4) Extravasation (those forming from extravasations).
    - (5) Dermoid (congenital and due to inversion of the cutis and to imperfectly closed fetal clefts).
    - (6) Parasitic (due to animal parasites).
    - (7) Cysts resulting from necrotic and degenerative changes.

[1] See foot-note, p. 320.

CYSTS.

A **cyst** consists of a connective-tissue membrane or supporting wall lined by epithelium or endothelium, and forming a cavity the contents of which may be fluid or semifluid, uniform in composition, or made up of a mixture of similar or dissimilar substances.

When the wall of the cyst is passive and influenced by the retained or extravasated contents in a mechanical way only, the cyst is said to be *simple* or *unilocular*. When several simple cysts occur together, all arising from the same cause, and identical in structure, they are called *multiple cysts*. When one cyst springs from the wall of another and thus gives rise to a second or a third cyst, the process resembling proliferation, the resulting cysts are known as *proliferous cysts;* the cyst walls may be destroyed by pressure (reciprocal), and thereby many of the cyst cavities communicate. When the cysts remain distinct, they are spoken of as *multilocular*. When the cysts communicate, they are sometimes said to be *cavernous*. When the lining membrane of the cyst develops papillomatous masses, the process is called *papilliferous*.

Classified by the cause and process of development cysts may be divided into: (1) *Retention cysts;* (2) *exudation cysts;* (3) *cystomata;* (4) *extravasation cysts;* (5) *dermoid cysts;* (6) *parasitic cysts;* (7) *cysts resulting from necrotic and degenerative changes in solid tissues.*

1. Retention Cysts.—These include all cysts due to occlusion of excretory ducts of glands with accumulation of glandular secretion and exudative fluids in the closed cavity resulting from obstruction of the passage by which, normally, evacuation occurs. Among the most common are: sebaceous cysts (wens); mucous cysts; salivary cysts (ranulæ); milk cysts (galactoceles); seminal cysts (true spermatoceles); nephric cysts (see Cysts of the Kidney); cysts of the gall-bladder or biliary passages; pancreatic cysts (pancreatic ranulæ), etc.

The wall of such cysts is composed of condensed and thickened connective tissue, and the lining cells are epithelial. The contents are derived from the functional activity of the gland structure, altered by absorption of a part of the fluid and by the degenerative changes that the cellular elements of the cyst wall may have undergone. When the duct obstruction first occurs, the accumulating fluid is a product of secretory activity of the gland; if the obstruction be complete, normal secretion soon ceases, the gland undergoes degenerative and fibrous changes, and irritation gives rise to inflammation of the cyst wall and the formation of an exudate which rapidly replaces the fluid at first accumulated. The change in the physical and chemic characters of the cyst contents is facilitated by osmosis. Not uncommonly cysts of this class eventually contain none of the materials characteristic of the gland in, or from which they arise: *e. g.*, the fluid found in the kidney in hydronephrosis may contain no body characteristic of the renal secretion. (See Hydronephrosis.)

2. Exudation Cysts.—These embrace cysts arising from accumulation in closed cavities not supplied by any excretory ducts or analogous structures. Such cysts are typified in the accumulations in bursæ, tendon-sheaths, the tunica vaginalis testis (hydrocele), canal of Nuck, etc The cyst wall is formed by thickened connective-tissue membrane

lined with endothelium; the sac or wall may be calcareous, cartilaginous fibroid, chondroid, or even osteoid. The contents are usually a clear limpid, serum-like liquid, but the fluid may be viscid or semigelatinous, or the cyst may contain solid bodies resulting from changes in the wall and desquamation or exfoliation into the cavity.

3. **Cystoma**[1] (*hygroma* or *hydroma*) is a cyst resembling the preceding, except that it is of new formation. The wall is of mesoblastic origin, lined by a flattened layer of connective-tissue cells (endothelium) The contained fluid is usually clear, straw-colored, slightly albuminous, and of low specific gravity; rarely, the fluid may be colored, cloudy, or, as a result of hemorrhage, grumous and possessing a dark, chocolate color. As to site, cystomata are most frequent in the neck (hydrocele of the neck) and in the axillæ (hydroceles of the axillæ); although infrequent, they have been observed in the subcutaneous structures elsewhere—back, belly, and even the extremities. By reason of their being most commonly congenital, occasionally associated with macroglossia, and on account of their close resemblance to the dilated lymph-spaces of the frog, it is believed by many that they arise from dilatation of the lymph-spaces; this view, if correct, would place them with the cavernous lymph angiomata (p. 347).

On three occasions the writer has seen cystoma of the liver; they were presumably congenital, and had been mistaken for sarcomata. One of the patients died from hemorrhage into the cyst, and the others from intercurrent maladies. The three were children, aged three, five, and six years respectively. It is not uncommon to find these cysts cavernous, with cavities of various sizes communicating with one another through one central space. The rule, as stated, that the specific gravity of the contained fluid is low, has occasional exceptions, as, in rare instances, the fluid may be as dense as the white of an egg, and so tenacious that it will not flow through an ordinary cannula introduced in tapping.

The most frequent site of a cystoma is in the ovary. Such tumors may be unilocular,—that is, made up of a single cyst cavity,—or they may be multilocular. The multilocular ovarian cystomata usually contain one, two, or more large cysts and numerous smaller cavities. As a result of reciprocal pressure, there may be more or less destruction of the septa, and numerous loculi may communicate with one another, forming a cavernous cyst, within the cavities of which the fluid is lodged. Certain of the ovarian cystomata develop papillary ingrowths, projecting from the inner membrane of the cyst wall as wart-like excrescences, which may be small or scarcely recognizable, or, on the other hand, may form large accumulations within the cyst cavity. As a rule, papilliferous cystomata are multilocular; less commonly they are unilocular. The lining membrane of ovarian cystoma is usually composed of columnar epithelium, which in some cases may be of the tall variety. Ciliation is rare. External to the epithelial stratum the wall is composed of fibrous connective tissue, which may contain myxomatous elements, and at times masses of gland tissue. In the presence of the latter element the tumors are called *cystadenomata*, and are usually papilliferous. Cystomata sometimes become infected and suppurate; usually this accident is disastrous, most of the patients dying. Werth, Pitha, Wal-

[1] Smith, "Medicine," September, 1903, p. 662.

gren, and Zantchento[1] have reported suppuration of ovarian cysts occurring as complications of typhoid fever; in most of the recorded instances the cysts were dermoids, but the ordinary type of ovarian cystoma may be similarly affected.

As a rule, ovarian cystoma is the largest cyst observed in the human body. Dr. Elizabeth Reifsnyder has reported the removal of an ovarian cyst containing 85 liters (approximately 88 quarts) of fluid and weighing 83 kilos (169 pounds); the patient weighed but 38 kilos (77 pounds). The tumor was unilocular, the empty sac weighing 3.2 kilos (6½ pounds).

4. **Extravasation Cysts.**—This variety of cyst is formed around distended or ruptured vessels, or in areas of hemorrhage, and may occur in any tissue. *Hematocele*, or any form of *sanguineous cyst*, is properly classed with this group. The cyst wall is usually thin, and its inner surface smooth; but the reverse may be true. In rare cases the internal surface of the cyst wall is fasciculated. The inner stratum of the connective-tissue investment of the cyst is first formed by the dissociated connective tissues; later these may be replaced by an endothelial covering. Rudolf[2] fully describes the hematomata that occur in the mesentery as a result of direct injury to the abdominal wall or indirect trauma, as by falls; these cases usually terminate fatally. As a result of injury during birth hematomata are sometimes seen in the sternocleidomastoid muscle of the new-born. By some writers the intrafollicular and intraparenchymatous hemorrhages in the ovary (ovarian apoplexy) are classed with the hematomata. As a result of injury, or disease of the vessels, meningeal hemorrhage sometimes gives rise to hematoma, which may be subdural or extradural. A special form of this condition, called hemorrhagic pachymeningitis, is discussed in the chapter on diseases of the Nervous System. Cysts occasionally occur through the extravasation of fluids other than blood; the accumulation of urine in the perineum, following rupture of the urethra, is a type of such cysts.

5. **Dermoid cysts** are always of congenital origin, and arise as the result of cutaneous inclusion, or in consequence of the inclusion of a blighted ovum. The wall may contain all the elements of the cutis, may be thick or thin, and not uncommonly shows a slight growth of hair; the cells lining the interior of the sac are, of course, epithelial. The contents are usually sebaceous matter and a varying amount of hair; occasionally, teeth are found. When situated in the ovary, testicle, brain, eye, throat, or abdominal cavity, developing bone or cartilage may be contained within the cyst cavity; these distinctly connective-tissue products indicate the possibility of such cysts arising from fetal inclusion. Occasionally, dermoid cysts contain fat the melting-point of which is below the normal temperature of the body. The author examined one such cyst. The tumor had evidently developed in the region of the ovary; the wall was so dense and calcareous that a saw was necessary to open the mass. The temperature of the body was still comparatively high, and the oily, fluid contents, which flowed from the interior of the cyst, immediately congealed on coming in contact with cold water. A similar tumor of the ovary has been described by Thoma. Dermoids

[1] "Rousski Vratch," 1903, No. 30.
[2] "Beiträge z. klin. Chir.," xliii, No. 3.

containing distinct connective-tissue bodies, such as cartilage and bone, are termed *compound dermoids*, thereby distinguishing them from dermoids containing no connective-tissue elements; the latter are called *simple dermoids*. The most common sites are near the orbit, the root of the nose, the angle of the jaw, the floor of the mouth, around the sheath of the carotid vessels, near the anus, and the sacrococcygeal and ovarian regions. There can be no doubt that most of the dermoids occurring in the body cavity, and sacral and perineal regions, belong with the teratomata. (See page 363.) Following the observations of Wilms, the tendency has been to call such tumors **embryomata.**[1] When two layers of the blastoderm are represented by structures in the growth the term **bidermoma** has been applied; when three layers are present, **tridermoma.** Sometimes these masses contain fully formed organs, such as a jaw, finger or hand, part of the thyroid gland, etc.

Closely related to the dermoid cysts but entirely distinct from them are the so-called **traumatic dermoids** which develop in wounds. These cysts are due to the inclusion of the epithelial layers of the skin or mucous membrane within the healed wound. Klar calls them **epidermoids.**[2]

6. Parasitic Cysts.—When any animal organism, capable of surviving in the tissues, gains ingress, a cyst is likely to ensue; some such parasites inevitably give rise to cysts, others not always. *Trichinæ*, when settled, develop a small cyst that rapidly becomes calcareous. (See p. 204.) *Coccidia* invading the liver induce a similar condition. (See p. 184.) The most important parasitic cyst in man, so far as our present knowledge goes, is the **hydatid.** This cyst arises as the result of the lodgment of the larvæ of the Tænia echinococcus in the tissues. The embryo is first converted into a cyst containing a clear fluid. The wall possesses two layers of its own, to which is added a layer resulting from the reaction of the surrounding elements. From the inner layer of the cyst—the endocyst—buds are developed that give rise to daughter cysts; other cysts develop in a similar way from the daughter cysts, and constitute what are known as granddaughter cysts. These cysts are, therefore, proliferative. The fluid of the cyst is usually nonalbuminous, slightly saline, and clear; its specific gravity is less than 1010, and it may contain sugar. Such cysts are likely to become inflamed, to suppurate, or to rupture, all of which terminations are unfavorable. If the parasite dies, the cyst may inspissate. It is not an exceptional thing to find these inspissated cysts in the liver; the contents are usually putty-like, occasionally crumbly, and frequently contain the hooklets. Inspissation represents a cure, but, unfortunately, other terminations may occur; the cyst may rupture into a closed cavity, as one of the serous cavities; rupture externally or into a bronchus or other hollow viscus occurs. A most dreaded termination is suppuration. (For consideration of the forms of hydatid cysts, diagnosis, and demonstration of hooklets, and for illustrations, see pp. 198 to 201.)

Cysticercus Cellulosæ, the larval form of the Tænia solium, gives

[1] See Clark, "Progressive Medicine," June, 1902, p. 223. Anspach, "Proceed. of Path. Soc. of Phila.," Nov., 1903, p. 209. Lecène, "Annal de Gynecol. et d'Obst.," Jan., 1904, p. 14. Hue, "Rev. Méd. de Normandie," July 25, 1904. Lejars, "La Sem. Méd.," Sept. 21, 1904.

[2] "Münch. med. Woch.," April 19, 1904, p. 705. Also Dujarier and Lecène, "La Presse Méd.," April 16, 1904, p. 241.

rise to small bladder-like cysts, which may be widely distributed. In the pig, the usual intermediary host, the cysts are about the size of a pea, and may be scattered throughout the tissues, producing a condition commonly known as "measled" or "measley" pork. (See p. 197.) In man the cysts occur in the muscles, brain, and spinal cord; occasionally, they may be recognized by the ophthalmologist in the chambers of the eye.

7. **Cysts resulting from necrotic and degenerative changes in solid tissues** include the cavities, found particularly in neoplasms, and brought about by hemorrhage, liquefaction necrosis, and other forms of softening[1]; the cavities containing fluid, sometimes observed in solid organs, such as the spleen and brain, and due to the imperfect removal of liquefied areas resulting from infarction, would properly be classed with this group. The liquid present in such cysts may contain altered blood pigment produced by hemolysis, and granular matter resulting from cellular disintegration.

[1] See page 25c.

CHAPTER XIII.

TEMPERATURE CHANGES.[1]

INTOXICATIONS. INFECTIONS.

The temperature of the human body remains practically constant, or about so, at 37° C. There are normally for each individual certain variations above or below the mean for the twenty-four hours; the maximum fall, in health, rarely exceeds 0.5° C., and is, for most persons, always at, or near, the same hour of the day; the same is true of the daily rise, so that between the daily maximum and minimum there is commonly about 1° C. of fluctuation. This daily curve of the temperature follows nearly the same course each day, so that the maximum is reached between 4 and 6 P. M., and the minimum between the same hours A. M.; this cycle for any given individual is nearly uniform, but no two persons are likely to have identical thermic curves. The following table, from Thoma, compiled by Jürgensen and Liebermeister, indicates the usual variations in body-temperature at different hours in the day:

Time of Observation.	Temperature in the Rectum. (*Jürgensen.*)		Temperature in the Axilla. (*Liebermeister.*)	
	F.	*C.*	*F.*	*C.*
In the morning in bed,	(98°)	36.6°	(97.8°)	36.5°
Before breakfast,	(98.18°)	36.7°	(98°)	36.6°
After breakfast,	(98.36°)	36.8°	(98.7°)	37°
In the forenoon,	(98.8°)	37.1°	(99.18°)	37.3°
Before lunch,	(99 18°)	37.3°	(99°)	37.2°
After lunch,	(99.36°)	37.4°	(99.18°)	37.3°
In the afternoon,	(99.5°)	37.5°	(99.36°)	37.4°
Before dinner,	(99.7°)	37.6°	(99°)	37.2°
After dinner,	(99.36°)	37.4°	(98.8°)	37.1°
Before going to bed,	(98.8°)	37.1°	(98.36°)	36.8°
During the night,	(98.7°)	37°	(98°)	36.6°
	(98.36°)	36.8°	(97.18°)	36.2°
	(98.36°)	36.8°	(97.18°)	36.2°

The hypotheses and theories presumed to explain the mechanism of temperature regulation are based upon certain well-established facts. Heat, representing cellular or tissue activity, is generated within the body by the oxidation of supplied or stored food, or of the tissues themselves, is distributed largely by the blood, and is lost chiefly from the skin and respiratory mucous membrane. The regulation of the body-temperature must be through means addressed to one of three agencies: heat production, distribution, or dissipation.

[1] A very full bibliography of the subject is given by Chantemesse and Podwyssotsky, "Les Processus Généraux," 1905, vol. ii, p. 500.

Heat production occurs in every organ and tissue, but the greatest thermogenic activity is manifested in the muscles, including the heart, and in the large glandular viscera: for example, the liver. The greatest heat production occurs in the voluntary muscles, including those of respiration. The heart muscle is presumed to afford a considerable supply of heat in the same manner as the other muscles, and, in addition, transmits force, which is indirectly converted into heat by the friction of blood against the cardiac walls and also against the walls of the arteries and capillaries, through the resistance of which the blood-pressure is largely maintained. The fact that the blood rises in temperature after passing through the liver is not surprising when the remarkable glandular activity of that organ is taken into consideration.

The distribution of the blood is profoundly influenced by the nerves supplied to the arterioles, and, as the dissipation of heat is largely dependent upon the distribution of the blood, the influence of vascular innervation upon heat loss is one of the most important elements to be estimated. Exactly what determines the action of the vasomotor nerves in the regulation of temperature is one of the unsolved problems in normal and morbid physiology. It would appear that there is somewhere a center, possibly more than one, that presides over the body-temperature by regulating heat dissipation at least, if not its production, but probably both. The theory of heat regulation by the nerves implies a heat-regulating center (**thermotactic center**), with nerves controlling heat production (**thermogenic nerves**), nerves controlling heat dissipation (**thermolytic nerves**), and, possibly, nerves that influence heat-producing tissues in a way antagonistic to the thermogenic nerves (**thermo-inhibitory nerves**). This complicated system is assumed to have its center in the medulla; this center, acted upon by certain agents, manifests disturbance through the fibers of some of the nerves indicated. In addition to one center, or possibly more, in the brain or the medulla, there may be in the cord, or even in the larger ganglia, subsidiary centers influencing a region, or regions, only. While the theory of heat regulation by the nervous system may be considered far from demonstrated, the facts that no attempt at heat regulation is made in animals possessing an indifferently evolved nervous system; that lesions of the higher evolved nervous system are followed by alterations in temperature regulation; and that the temperature, both normal and abnormal, may at times be influenced by hypnosis, would each seem to indicate relations between heat regulation and the nervous system that can not be ignored. The production of heat by the oxidation of food and of tissue elements, the distribution of the heat generated, and its final dissipation, are complicated phenomena that, with our existing knowledge, can be but imperfectly contemplated.

Hypothermia (Subnormal Temperature).—A temperature below the mean normal of the active period of life occurs in some forms of anemia, and in myxedema, chronic heart-disease, and cancer, follows shock and severe hemorrhage, is present in some forms of exhaustion or adynamia, and frequently succeeds marked elevations of temperature, particularly if prolonged; thus, after typhoid fever and pneumonia a period of subnormal temperature is often seen. Starvation or prolonged exposure to low temperatures, or the two combined, may give

rise to a reduction in the body-temperature. The explanation of this condition lies probably in the lessened heat production, although instances occur—as in the occasional cases of great cutaneous activity after hemorrhage and shock, and in cases of exposure to extremely low temperatures—in which more heat may be lost than normal; such a source for subnormal temperature, however, is not common. The reduction of temperature may also be caused by the circulation of certain poisons in the blood, as in diabetes, in which the temperature may sink 5° C. or even more. In this condition both heat production (thermogenesis) and heat dissipation (thermolysis) are probably at fault, the control and equalization of the two by the thermotactic power having been perverted by the influence of a noxious agent circulating in the blood.

Pyrexia.—Under certain conditions there arises a chain of phenomena which the clinician recognizes as *fever*. There is disturbance of a number of functions: appetite, secretion and excretion, the circulation, respiration, and, in many cases, the central nervous system, show marked perturbation. With one or more of these phenomena there occurs the one constant element of fever—*elevation of temperature* (**hyperthermia**). In moderate cases the temperature reached may not exceed 39° C.; in more severe cases it may reach 41° C., and in grave cases may go beyond 42° C. Temperatures exceeding 55° C. have been observed.[1]

Causes.—Prolonged exposure of a warm-blooded animal to a temperrature in excess of its normal commonly induces hyperthermia. The rapidity of occurrence and the degree of hyperthermia are dependent upon the height of the temperature to which the animal is exposed, and are influenced by the medium through which the heat is applied. The temperature-rise is most marked if the animal be submerged in water; next in point of efficiency is air containing abundant moisture, while dry air is least efficient. Absence of moisture lessens the probability of the occurrence of hyperthermia, and individuals may be subjected to comparatively high temperatures in dry air and yet escape heat-stroke. In many of the industries laborers are exposed for a varying period of time to comparatively high temperatures; if such exposure be prolonged or if moisture be present, heat-stroke may ensue.

Hyperthermia may be produced by diseases or injuries of the central nervous system; puncture of the corpus striatum, many indefinite lesions of the bulb, certain cortical irritations, and injuries involving areas in the upper cervical cord may be followed by hyperthermia. Hale White has recorded two cases of hemorrhage into the corpus striatum associated with a rise of temperature, most marked on the opposite side of the body, lasting in one case four days, and in the other, twelve days.

There can be no doubt that the most important causes acting in fever production are *bacteria and their products*.[2] That the germs are not the essential element may be shown by the production of artificial temperature-rises by the injection into animals of filtered and also of sterile cultures of certain bacteria. The introduction of preformed poisons

[1] See Lord, "Brit. Med. Jour.," Nov. 15, 1902, p. 1578. Bunbury, "Brit. Med. Jour.," July 25, 1903, p. 193. Oettinger, "Colorado Medicine," May, 1904. Wood, "Med. Record," June 25, 1904, p. 1041.

[2] See bacterial poisons, p. 87.

into the system gives rise to a chain of symptoms, the condition being termed an *intoxication*.[1]

The febrile and other disturbances associated with the **microbic intoxications** are not purely the outcome of laboratory experiment, but constitute important clinical phenomena. The symptoms of some of the infections are purely the evidence of intoxications; in diphtheria the bacillus may be limited, even in fatal cases, to proliferation on the surface of the mucosa, many of the symptoms, and all the lesions occurring elsewhere than at the point of growth, result from the dissemination of the toxin through the lymphatics and its distribution eventually by the blood. A simpler example of pure microbic intoxication, one frequently cited, is the infection of a blood-clot in the uterus following labor. The bacteria generating the poison in the blood-clot may never gain ingress to the living uterine tissues, much less to the circulation, but the products of microbic life pass, by absorption, into the blood, through which, directly or indirectly, they induce the phenomena of intoxication. A retained blood-clot between the flaps in a recent amputation, becoming infected, acts in a similar manner. By reason of this danger, in addition to its mechanical interference with healing, surgeons recognize the necessity of avoiding "dead spaces" in which infection may be favored by lessening the protective influence of living tissues. Commonly, the organisms active in the production of bacterial intoxications are pathogenic in the true sense of the word. It is not to be forgotten, however, that bacteria normally unable to infiltrate living tissues, and hence properly classified with nonpathogenic organisms, may pullulate in dead tissue, and may elaborate poisons the absorption of which gives rise to grave intoxications. The intoxication resulting from the absorption of microbic products is known as **septic intoxication,** or **sapremia,** and the element absorbed—the bacterial product—is termed **pyrogenous.** A peculiar fact, often observed, is that in the brain the products of bacterial life may not induce fever. This may be explained in a number of ways. Growing on different culture media, bacteria produce alkaloids with varying pyrogenous activity, and in the brain-tissues the activity or character of the microbic toxin, by reason of some peculiarity in the pabulum supplied, may be changed; the very fact that the abscess involves brain-tissue, and that the same may be potential in controlling temperature or in modifying it, may make the accident of location a determining factor in its influence on body-temperature. Again, evidence is not wanting to show that dissemination of poisons is less rapid by absorption through brain-tissue, and this may in part explain the absence of fever in some cerebral abscesses; it fails, however, to offer any reason for the subnormal temperature at times observed.

The production of pyrogenous substances by animal parasites is well illustrated by the peculiar febrile phenomena of malaria. Experimental research into the exact nature of the fever-producing body elaborated by such organisms as the malarial parasite has not afforded any satisfactory conclusion, nor have we much to hope for in this direction until it becomes possible to study the parasite in artificial culture. It is commonly believed that during the segmentation of the protozoon there is elaborated a poison that brings about the rise in temperature.

[1] See p. 76.

While such a view may be satisfactory, in a sense, it is necessary to remember that the mere destruction of blood-cells may bring about fever, and when it is recognized that in malaria this process, hemolysis, is particularly active, we can not ignore the possibility of its bearing something more than an associated relation with the fever present.

Intoxications arise, however, without the intervention of micro-organisms, either animal or vegetable. In cocain-, strychnin-, and brucin-poisoning, and following the introduction into the circulation of certain animal poisons, as from snake-bites, stings of scorpions, etc., typical intoxications occur. Not in all of these is there elevation of temperature.

In addition to the toxic bodies introduced from without,—such as those just mentioned, and among which may be included mussel-poisoning,—intoxications may arise from poison generated within the body—**direct** and **indirect auto-intoxications.**[1] The latter include **enterosepsis,** or **copremia,** an intoxication occurring from the retention of intestinal contents, as in chronic constipation. The toxic material here is not wholly a microbic product, nor is it entirely the result of retention and absorption of noxious agents of purely animal origin, but is far more complex, including poisons derived from both sources.

There is another source of fever-producing or pyrogenous material in tissue dissolution and in the formation of certain exudates; the exudates thrown out in the process of repair, during the formation of blood-clots,—as around fractured bones and under similar conditions,—contain some agent that, by absorption, produces elevation of temperature. The chemistry and even the identity of the body is still a matter for speculation. Brieger noted the constant association of fever and fibrin formation, and surmised that both depended upon the presence of the ferment presumed to cause the separation of the liquor sanguinis into fibrin and serum; this view has been generally accepted. But numerous observations go to show that disintegration of other substances than the plasma can be attended by the liberation of disintegrative endogenous poisons. The rise of temperature that follows a surgical operation, the fracture of a bone, or an interstitial hemorrhage is presumed to be due to pyrogenous materials produced in the way just indicated. These fevers—**surgical aseptic fevers**—are not usually classed with the intoxications, although it is evident that they are essentially of that nature.

Local Infections.—In sapremia the poisons generated by the bacteria are elaborated outside of living tissues, and in septicemia the toxic bodies are derived from bacteria in the blood. Intermediate between these are the local tissue infections, in which the bacteria invade living tissue, from which the microbic poisons are absorbed into the circulation, either directly, through the capillary walls, or indirectly, by the lymphatics. In diphtheria the bacteria may reside on the surface of the mucosa only, the toxins disseminating beyond and inducing necrosis,—more dead tissue,—into which the bacteria grow. In some cases, however, the germs pass the dead membrane and infiltrate the living tissues; there is then a local infection of living tissues as well as a growth in the dead, or necrotic, adjacent structures. Erysipelas, abscess formation, the initial lesion of anthrax, and, under similar con-

[1] See classification of poisons and intoxications, p. 77.

ditions, many infections, are in part—primarily, at least—but local infections, with dissemination or absorption of the microbic products giving rise to the phenomena of an intoxication, the blood escaping actual invasion by the bacteria. The local infections, with systemic symptoms due to the absorption of toxins produced in the living tissues, stand intermediate between pure intoxications, such as sapremia, and the mycoses of the blood.

Any infection, whether localized or widely diffused, may be **simple**: that is, *single*, or due to but one germ, as a pure or simple infection by the streptococcus of erysipelas. A simple or single infection may be followed by the introduction of a second germ; the additional infection is known as a **secondary infection.** As an example of the last-named condition may be mentioned the infection of a tuberculous area with an organism of suppuration. A secondary infection may be followed by a **tertiary infection,** and so on. Again, a number of infections may occur, so far as we can determine, at one time; the process is then said to be **mixed infection** or **concurrent infections.** It is interesting to note that in the mixed and secondary infections it is not necessary that all of the bacteria present should belong to the pathogenic class. If one of the microbes be disease-producing and lead to tissue necrosis, the secondary infection may be by a saprophyte living upon the dead tissue resulting from the necrotic processes induced by the pathogenic organism As a rule, mixed and secondary infections are more grave than simple infections, because the additional ferments produced by the second germ can but intensify the dangers to which the patient is subjected.

The fact that nonpathogenic bacteria live and produce noxious elements in the necrotic tissues produced by pathogenic bacteria renders it possible to appreciate how dead tissue, or tissue with its protective powers in a state of abeyance, as after extensive bruising or laceration, may permit the growth of bacteria that, in less injured tissues or in healthy structures, would immediately succumb to the protective powers of the animal. For these reasons injured structures and tissues with greatly reduced nutrition may need a protection from infection not demanded by healthy tissues.

Bacteremia. Mycoses of the Blood.—In this condition the bacteria multiply in the circulating blood, in which their products are generated. The intensity of the septic phenomena is augmented by the greater production of the poison, and, not having even the barrier of protection afforded by the necessity of osmosis or absorption, they are enabled to engender lesions not presumed to occur—at least, not to the same extent—in either sapremia or local infection. The path of infection[1] may, as in surgical sepsis and puerperal cases, be self-evident. In othe instances it is impossible to determine exactly by what route the infecting organism entered the circulation; to this latter group Leube gave the name **cryptogenic sepsis.** The term **septicemia** was meant to cover, probably, some local infections, as well as mycotic invasion of the blood, but particularly infection of the blood by the organisms of suppuration. That the common pyogenic bacteria are not the exclusive source of septicemia is shown by the reported instances of clinically typical cases of the disease, without the presence

[1] See page 90.

of the pyogenic cocci, but resulting from the action of other bacteria, as the diplococcus of pneumonia, Bacillus typhosus, colon bacillus, Bacillus pyocyaneus, and other organisms. The microbes not only proliferate in the blood, but also, in occasional cases, are found pullulating on the walls (*mural implantation*) of some part of the circulatory system, as the valves of the heart in ulcerative or malignant endocarditis. This colonization on the walls of the blood-vessels, heart, sinuses, etc., may lead to the development of thrombi; and from these, emboli; or, possibly, massing of elements in the blood may lead to emboli—emboli formed in transit. The last is a questionable hypothesis. The emboli formed in blood, and containing bacteria, are, of course, septic, and at their point of lodgment engender the changes already considered when discussing embolism. The embolic production of an abscess, or of abscesses, is the essential element of **pyemia,** a disease recognized by surgeons as septicemia plus infected emboli to which are attributed the metastatic abscesses. (See Thrombosis and Embolism, pp. 270 and 278.)

The fever that accompanies the septic processes is peculiar, on account of the remarkable exacerbations, which usually occur daily; and, in the graver forms, on account of the addition of repeated **rigors** or **chills.** Rigors are not restricted to septic processes, but occur also after hemorrhage, occasionally after shock, and as a poorly understood purely nervous manifestation; they constitute the most marked phenomenon of the malarial paroxysm.

During the cold stage, or chill, there is a determination of the blood to the large glandular viscera and venous trunks; the skin is thus deprived of its normal heat by the deficiency of its blood-supply, and the cooling of the cutaneous nerves affords the explanation for the patient's sense of intense chilliness. That the low temperature is purely a cutaneous phenomenon is shown by the thermometer. If the temperature be obtained in such a way as to estimate the actual blood-heat,—as in the rectum, mouth, or axilla,—preventing heat dissipation at the point at which the temperature is being taken, the temperature is found to be above the normal. The deficiency of the cutaneous circulation lessens heat dissipation, and probably at the same time heat production is increased. Certainly, in some fevers there is an increase of heat production, as abundant evidence is not wanting to show that heat dissipation may be greater than normal, and yet that elevation of temperature may persist—a condition impossible without persistent overproduction. The rigors associated with reduction of surface temperature due to the exposure of the body to a medium the temperature of which is low, appear to be reflex phenomena, brought about by an attempt on the part of the economy to produce more heat in response to the recognized surface fall. They are to a certain extent under the control of the will. The amount of temperature reduction necessary to the production of a rigor is usually not over from 0.5° to 1° C. It is interesting to observe that in pyrexia a chill results whenever the surface temperature is from 0.5° to 1° C. lower than the internal temperature. After persisting a varying length of time, the chill ends by a return of the blood to the skin, and usually rapid heat dissipation, though by no means always, followed by a marked decline in body-temperature.

The *acme* or *fastigium* of the fever may be quickly reached; its duration may be brief, or, in other cases, the fever may persist at about the same point for a considerable length of time, usually showing slight matinal and vesper oscillation. The fever may disappear within a few hours (*crisis*) or may gradually subside, requiring many days (*lysis*).

Whether preceded by a chill or not, the acme of the temperature-rise is commonly followed by a progressive decline, associated with hyperactivity of the emunctories, particularly the skin. This gradual decline usually begins in the afternoon or early evening and progresses through the night, with the early morning temperature the lowest, the rise beginning at this time and reaching its height during the afternoon. During the twenty-four hours the fever may disappear, only to reappear in a few hours; this type is said to be *intermittent*. In the *remittent type* there is more or less marked remission, but no period of complete apyrexia.

The active causes producing this rhythmic alteration in temperature are obscure. It is maintained that the accumulation of pyrogenous material, and its tendency toward fever production in the system, is at first compensated by the thermotactic powers; eventually, the failure to excrete the poison as rapidly as produced permits of such excessive accumulation that the heat-regulating forces are inadequate to the task of maintaining a constant temperature. This is followed by a rise, which continues until the exhausted centers—which normally responded to slight temperature variations by adjustment of the mechanism between heat production and heat dissipation—respond to the more urgent demand for heat dissipation by a pseudo-crisis, during which the temperature falls. The depressed or exhausted center, not responding to the slight changes that would affect it in health, now permits another accumulation of heat, which again sets it off, the process being repeated day after day as long as the pyrogenous material is thrown into the circulation.

Paradoxic Pyrexia.—None of the hypotheses at present available explains satisfactorily the occurrence of what Dr. Savage has called "mad calorific areas." Such a condition is illustrated by a case reported by Knowling, in which at one time the temperature was 99.4° F. in the left axilla and 105° F. in the right. An explanation that at once suggests itself is that vascular dilatation on one side of the body or in a certain area permits ready access of the blood coming from the viscera, resulting in higher temperature, while a less active peripheral circulation in other parts of the body to a certain extent conceals the internal hyperthermia. Often there is no evidence of such vascular dilatation, and in the absence of phenomena that would favor this conclusion it would probably be wrong to accept it as final.

It has been held that thermolysis may be increased upon the opposite side, and hence the temperature-rise is marked upon the side in which thermolytic activity is diminished. With regard to this theory and to the opinion previously given, it can only be said that both are speculative, and that neither rests upon a basis of fact that would justify us in formulating a definite opinion at this time.

With the rise in temperature certain circulatory phenomena manifest themselves. Thus, for every degree Fahrenheit (0.55° C.) that the body-temperature rises, the pulse-rate is increased about ten beats. This

observation is approximately correct for elevations of temperature within two or three degrees, but with higher temperatures a greater rise occurs; Liebermeister showed that, for the 1° C. above 41° C., the number of heart-beats increased 27.

During the earlier stages of fever the *blood-pressure* is likely to rise also, but the early relaxation of the vasomotor nerves—probably due to exhaustion, degenerative changes, or inefficient nutrition—is followed by a fall in blood-pressure. More important than the disturbance of blood-pressure, although no doubt largely due to the same, is the *change in the blood distribution;* in fever the latter often varies greatly, as already stated when considering the dissipation of the abnormal heat. The large glandular viscera are not infrequently perceptibly altered by the increased amount of blood sent to them, and by its relative, if not absolute, stagnation in their interior.

Blood Changes.—The blood is materially lessened in nutritive value, partly as a result of the interference with assimilation, both primary and secondary, and partly from the destruction of the blood elements. The hemolysis is not usually manifest until the fever subsides, not having been marked previously by reason of the concentration of the blood, so that a blood examination during the height of the fever fails to disclose the loss of globular elements until, by dilution, after the fever has disappeared, the oligocythemia and oligochromemia become apparent.

Changes in Organs.—In considering alterations that occur in the tissues we are at once confronted with the difficult task of differentiating lesions that are due to the febrile process alone from lesions that are dependent upon the action of poisonous agents—such as toxins, etc.—that were themselves etiologic factors in the production of the fever. It is not improbable that many of the tissue alterations attributed to the rise in temperature alone are truly dependent upon the action of the poisons that brought about the fever. In addition to the changes in the blood, other tissues show marked alteration. The large glandular viscera, particularly the liver and kidneys, exhibit cloudy swelling; a similar change occurs in the muscles, the heart often manifesting the granular alteration of its fibers to the highest degree. Hyaline change in the muscles has also been observed. The adipose tissues sooner or later show wasting, and the nerve elements evince the granular and pigment alterations incident to exhaustion. The mucous membranes, that of the alimentary canal in particular, present granular and fatty changes. Many of the tissue changes may arise from contact with the poisons circulating in the blood; others are possibly due to the accompanying elevation of temperature and to associated disturbances of nutrition.

Beneficence of Pyrexia.[1]—Experimental evidence has seemed to demonstrate that a rise in the body-temperature may be, in certain infections, distinctly beneficial. In pneumococcous infection it has been found that resistance is increased by maintaining the animal at a temperature between 41° and 41.5° C. Similar results have been obtained with the streptococcus of erysipelas and with a few other organisms.

[1] Löwy and Richter, "Berlin. klin. Woch.," 1897, No. 9; also "Centralbl. f. inn. Med.," July 17, 1897. Löwit, "Centralbl. f. allg. Path. u. path. Anat.," Dec. 15, 1898. Beniasch, "Zeit. f. klin. Med.," Bd. xlv, Hefte 1 u. 2.

Rolly and Meltzer[1] have shown that phagocytosis increases in activity as the temperature rises from normal to 40° C., after which it regresses. They have also demonstrated experimentally that the production of agglutinins and bacteriolysins is more active in hyperthermic animals than in normal controls. Should further research establish the correctness of these observations, it is not impossible that we may have to revise, indeed reverse, our views as to the essential etiologic factors active in fever production. Thus, it may be shown that leukolysis and liberation within the body-fluids of antimicrobic substances belong to the protective phenomena, and that these bodies can bring about the elevation of temperature, which is itself a part of the reaction by which immunity is evolved. Investigations directed along this line may show that the temperature-rise accompanying the malarial paroxysm is the cause of sporulation, and that the latter is not the cause of fever, as at present is held. In the existing state of our knowledge such suggestions can scarcely be dignified by calling them even hypotheses; the fact that fever accompanies infection—indeed, seems to be its most constant companion—demands a better explanation than is at present available.

[1] Deut. Archiv. f. klin. Med., xciv, 1908.

PART III.

SPECIAL PATHOLOGY.

PART III.—SPECIAL PATHOLOGY.

CHAPTER I.

THE BLOOD.[1]

TECHNIC OF BLOOD EXAMINATION.

Examination of the Blood.—Blood is examined microscopically to determine the number and character of the corpuscles and their relative proportion, and the presence or absence of parasites, either vegetable or animal. Examination in the fresh, unstained condition should be followed by a study of stained specimens. Estimation of the hemoglobin is also of the greatest importance.

Obtaining the Blood.—The lower part of the lobe of the ear or the tip of the ring-finger, because of their accessibility, are the points usually selected for drawing the blood; other areas may be equally available. The region chosen should be free from edema, inflammation, or any other morbid process likely to give rise to the presence of other fluids that may become mixed with the flowing blood. Cleanse carefully the selected site, first with water, then with alcohol, rubbing briskly with a towel thoroughly to dry the part; this will induce hyperemia sufficient to cause free flow of the blood. With a lance-shaped needle prick the skin quickly and to a good depth. The author is averse to the continuous use of a single instrument, and therefore hesitates to recommend any of the many devices for pricking the skin. There is no reason for the repeated use of the same instrument. A pen, preferably of steel, with one nib broken off, as recommended by a number of observers, is cleanly and inexpensive, enabling one to use a different instrument for each observation. Let the first few drops escape and wipe them off, using for examination only the blood that follows. Have at hand at least a dozen cover-glasses, carefully cleaned in acid alcohol followed by alcohol and careful wiping; also four slides cleaned in the same way. A square cover-glass, gently warmed, not hot, is allowed to touch a small drop of blood; a droplet adheres, and the cover-glass is inverted, drop downward, on a warm, clean slide. As soon as the blood runs to the edge of the cover-glass, with a sable brush, cedar oil—conveniently obtained from the immersion oil that accompanies the microscope—or vaselin is painted around the edge to exclude air and to prevent drying. The slide is now ready for examination. A second and a third slide are prepared in the same manner. A very satisfactory method for obtaining slides, with minimal exposure of the blood to the air, is to take a thoroughly clean slide and cover-glass,

[1] The literature and full clinical studies of diseases of the blood will be found in Da Costa's "Clinical Hematology," Phila., 1905.

so adjusting them that the cover on top of the slide comes even with the edge; when the edge is presented to the drop of blood, barely touching it, the blood, by capillary action, flows between the two glasses. Slides so prepared can not be so readily sealed, but when the space between the cover-glass and the slide is completely filled, drying of the serum at the margin more or less perfectly excludes the air. Such temporary mounts will not keep, and must be examined at once, using first low powers and then higher. To make **films,** one cover-glass is touched to a drop, so that the center of the glass receives the droplet; immediately, a second cover-glass is dropped on the first, care being taken that the corners do not coincide; if the glasses are clean, the blood quickly flows to the edge; at once separate the two covers by sliding them apart, carefully avoiding any lifting motion; dry quickly, but avoid heating while moist. From each case, at least eight or ten spreads should be prepared in this way. Some prefer glass slide films made by drawing one slide, to the end of which adheres the blood, over a second slide at an angle of 45 degrees, the blood being in the acute angle. If certain staining methods are to be employed, the films must now be fixed.

Fixation of Films.—The method usually advised for fixing is by heat, as in a hot-air oven or sterilizer at 125° to 140° C. for twenty to thirty minutes, the lower temperature requiring the longer time. Ordinarily, satisfactory results will be obtained if the temperature be slowly raised to between 125° and 130° C., the heat withdrawn, and the oven permitted to cool slowly. Ovens constructed on the principle of hot-air sterilizers, (see Bacteriologic Technic) are best adapted for the fixation of films. In the absence of an oven a copper plate or strip is convenient; a strip from 5 to 10 cm. wide and from 20 to 30 cm. long, supported over a flame and protected from drafts of air, answers very well. The flat-iron-shaped table (Fig. 30, p. 35) may be used in the same way. Placed at one end, the flame soon heats the strip so that at any point a fairly constant temperature is maintained. By dropping water on this plate at various points a place is found where water boils; drop the cover-glass on this point, turning the film side down; about twenty minutes will be needed for fixing. A number of competent observers fix the dried films in the same manner as spreads of bacteria. (See Bacteriologic Technic.) For a finer study of the nuclei in blood-cells, and when recognition of the granules is not so important, some of the fixatives recommended in Chapter II, Part I, may be used; solutions containing bichlorid of mercury, and also the osmic acid solutions, may find special application. (See p. 34.) Cover-glass films may be fixed by immersion in a mixture of equal parts of absolute alcohol and ether for half an hour, followed by drying. After fixation by any of the foregoing methods the covers may be stained at leisure.

Staining.—Properly prepared and fixed films are grasped in the cover-glass forceps used for staining bacteria. The stain may be applied to the cover, or the cover, grasped in Kalteyer's forceps, may be immersed in a dish containing the stain. Slides had best be placed in jars of the stain.

Stains.—Wright's Stain.—This is one of the latest and in some respects the best of the numerous methylene-blue-eosin stains now in common use, other well-known members of the group being those de-

vised by Nocht, Goldhorn, Jenner, and Leishman.[1] The chief points of superiority are that special fixation of films is not required, and blood-plates, basophilic granules, and malarial parasites are well stained. The preparation of Wright's stain is a complex procedure and need not here be given. The technic for employing it is briefly: (1) Cover thin, air-dried films with the stain for one minute. (2) Add to the stain water, drop by drop, until an iridescent scum forms on the surface; for ⅞-inch square cover-glass films, 4 to 8 drops usually suffice. Allow the diluted stain to act for two or three minutes. (3) Wash with water, preferably distilled, until the film becomes pink or yellow in color. (4) Blot with filter-paper, air dry, without heat, and mount in balsam. Results: Erythrocytes, orange or pink; nuclei of leukocytes and erythroblasts, dark blue to lilac; cytoplasm of lymphocyte, robin's egg blue, of hyaline cell, pale to dark blue; neutrophile granules, reddish-lilac; eosinophile granules, pink; basophile granules, blue to royal purple; blood-plates, pale blue with dark lilac or blue granules. Films more than a few weeks old are apt to yield unsatisfactory results; this may be partially overcome by fixing with the undiluted stain for at least two minutes and staining four or five minutes after dilution.

Ehrlich's Triacid Stain.—A mixed powder for the preparation of Ehrlich's stain is on the market, but solutions prepared from it are rarely satisfactory; for this reason it is recommended that the stain be made from concentrated aqueous solutions of the dyes. The solutions are all to be saturated, and the quantities given will insure saturation from almost all samples, but as the dyes vary in solubility, different samples may require slightly more or less of the dye. As it is best not to filter, and as only the supernatant fluid is to be used, it will be found convenient to make up all these stains in tall, narrow bottles and, while more expensive, Grübler's stains had best be used.

1. Saturated aqueous solution of orange G:

Orange G,	6 gm.
Distilled water,	100 c.c.

2. Saturated aqueous solution of acid fuchsin:

Acid fuchsin (fuchsin S),	9 gm.
Distilled water,	100 c.c.

3. Saturated aqueous solution of methyl-green:

Methyl-green (OO cryst.),	6 gm.
Distilled water,	100 c.c.

These stock solutions keep well. The mixed stain prepared from them has not such good keeping qualities, and, while not ripe for the best results under one week, after two or three weeks usually does not stain so well; occasionally, however, a sample may give fairly good results for months. A little experience enables one to see which of the three dyes is deficient, and by adding a trace of the required stain, the mixture can be improved. Hardly any two blood cases stain alike, and, for the best results, slight changes in the formula may be made in order to overcome this defect. Ehrlich's formula, as given

[1] For an admirable summary of these stains see article by Baumgarten, "American Medicine," January 2, 1904.

by Cabot, and the Johns Hopkins formula, as given by Simon, are as follows, made from the foregoing stock solutions:

Ehrlich's Formula.

Saturated watery solution of orange G,	6 c.c.
" " " " acid fuchsin,	4 "

To these add a few drops at a time, shaking between each addition,

Saturated watery solution of methyl green,	6.6 c.c.

Then add:

Glycerin,	5 c.c.
Absolute alcohol,	10 "
Water,	16 "

Shake well for one or two minutes. Let stand twenty-four hours.

Johns Hopkins Formula.

Orange G solution,	13 to 14 c.c.
Acid fuchsin solution,	6 " 7 "
Distilled water,	15 "
Absolute alcohol,	15 "
Methyl-green solution,	12.5 "
Absolute alcohol,	10 "
Glycerin,	10 "

After the methyl-green is added, stir while remainder of alcohol and glycerin is slowly mixed with the other constituents.

In the preparation of the stain it is important that the definite order given be followed in the mixing of the foregoing ingredients. Stain the fixed films for from two to five minutes, wash in distilled water, dry, and mount in balsam. Results: Erythrocytes, orange; nuclei of leukocytes and erythroblasts, blue or greenish-blue; neutrophile granules, lavender; eosinophile granules, copper red; basophile granules, unstained.

Kanthack and Hardy especially recommend a 0.5 per cent. solution of eosin in seventy per cent. alcohol; stain for thirty seconds, rinse in water, dry by gentle pressure between folds of filter-paper, pass three times through the flame, and counterstain in *Löffler's methylene-blue solution.* (See p. 48.) For the demonstration of structurally imperfect red cells a one per cent. solution of eosin (water soluble) in fifty per cent. alcohol, followed by washing in water and then by hematoxylin, gives satisfactory results.

A special stain for the "mast cell" is prepared as follows:

Saturated alcoholic solution of dahlia, filtered,	50 parts.
Glacial acetic acid,	10-15 "
Distilled water,	100 "

Stain for twenty-four hours, wash in water, dry, and mount in balsam. Satisfactory stains of this cell may be obtained by the use of carbol-toluidin-blue (p. 48) applied for a few minutes, followed by differentiation in glycerin ether (p. 49); the granules are more sharply outlined by this method, and the results are more uniform.

Iodin Reaction.—The term iodin reaction, or **iodophilia,** is used to designate the reaction occurring under certain conditions when the

blood is subjected to the action of iodin. The solution usually employed consists of:

Iodin,	1 part.
Potassium iodid,	3 parts.
Gum arabic,	50 "
Distilled water,	100 "

An air-dried film of blood is covered with this syrupy solution, which is allowed to act for two or three minutes; the excess is then drained off and the cover-glass placed blood-side downward on a slide. A more rapid, but less neat, method is to place a large drop of the solution near one end of a slide and invert upon it the cover-glass, which in two or three minutes is moved to the center of the slide, leaving behind the thick layer of fluid. These preparations, being mounted in the staining medium, are not permanent. Examined under the oil-immersion lens, the red cells, normal leukocytes, and blood-plasma are found to be stained a uniform pale yellow. A positive iodin reaction consists of the presence of variable sized granules, ranging in color from brownish-yellow to deep brown, which, in location, are intracellular or extracellular. The former are almost exclusively within the polymorphonuclear leukocytes. Instead of distinct granules, there is in some instances a diffuse brownish discoloration of the cytoplasm. The extracellular granules, less often found and relatively of little importance, are free in the plasma. The significance of the reaction is variously estimated. It is observed in cases of sepsis, and most frequently when suppuration has occurred, but is not a positive indication of the presence of pus. It is also found quite constantly during the course of pneumonia, pulmonary tuberculosis, malignant disease, certain of the grave anemias, and occasionally in other affections. Apparently depending upon degenerative changes in the leukocytes, the real diagnostic value of this reaction is not as yet determined.

Staining Diabetic Blood.—Bremer's observations on the peculiar stain reactions of diabetic blood appear to deserve much more consideration than they have received. From a number of experiments in the author's laboratory I am convinced that certain information may be obtained by Bremer's methods, and that the test is deserving of consideration. It requires constant control under nearly all conditions, and hence every examination should be verified by applying the test to blood known to be normal as well as to the suspected specimen. Thick films of the blood under examination and control films, both prepared in the usual way, are fixed by heat at a temperature of 135° C. The two covers are then grasped back to back, so that both films are exposed, and are immersed in either a one per cent. watery solution of Congo red or a one per cent. watery solution of Biebrich scarlet for about two minutes. The films are then washed in water and dried. Congo red stains the normal blood and not the diabetic; Biebrich scarlet stains the diabetic blood and not the normal. Other anilin dyes may be applied in a similar manner. The important point to be recognized is that diabetic blood is never stained to the same degree, and often not the same shade, as the normal blood. The reaction is sometimes obtained in conditions other than diabetes.

ESTIMATION OF THE HEMOGLOBIN.

Gowers' Hemoglobinometer.—This apparatus consists of two glass tubes of exactly the same size; one contains a standard solution, the tint of a dilution of 20 c.mm. of blood in 2 c.c. of water (1 : 100).[1] The second is graduated into 100 degrees, and is arranged to contain 2 c.c. (a hundred times 20 c.mm.), or more, when the percentage of hemoglobin is above 100.

Twenty cubic millimeters of blood are measured by the capillary pipet and ejected into the bottom of the graduated tube, a few drops of distilled water being placed first in the latter. The mixture is rapidly agitated by a rinsing movement, and distilled water is then added, drop by drop, until the tint of the dilution is the same as that of the standardized tube. The degree of dilution indicates the amount of hemoglobin, and may be read off from the graduated tube.

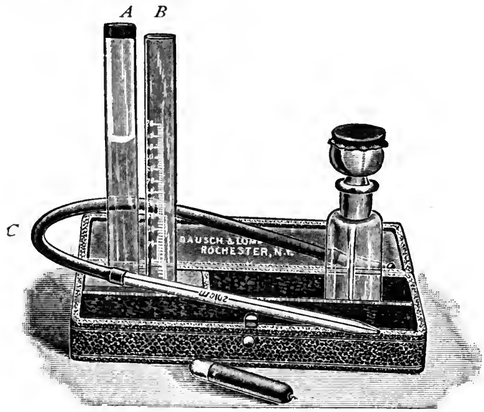


FIG 213.—GOWERS' HEMOGLOBINOMETER, IMPROVED FORM.
A and *B* are flattened tubes, *A* being permanently sealed and containing the tint standard; *B* is graduated and is used for diluting the blood. *C* is a pipet for measuring the blood, as directed in the test. Just in front of the case is shown the needle usually recommended for puncturing the skin. The dropping-bottle shown in the illustration contains distilled water for diluting the blood.

Von Fleischl's Hemoglobinometer.—The standard of comparison in this instrument is an elongated wedge of glass, tinted with Cassius' golden purple, and mounted movably beneath a platform or stage like that of a dissecting microscope. In the center of the platform is a circular opening, through which the light f om a candle or lamp is reflected upward from a disc of plaster-of-Paris.

The wedge of glass underlies one-half of the circular opening in the platform. Above the wedge, and exactly over the circular opening, rests a metallic tube, 1.5 cm. long, with a vertical metallic partition and a glass bottom. One-half of the tube overlies the wedge and receives its light through it. This half is filled with distilled water, and in the other half is placed the mixture of blood and water. The blood is received from the finger into a minute glass tube by capillary attraction (automatic pipet) and is placed in the proper compartment, thoroughly mixed with water,—care being taken to see that the measuring tube is washed free from blood,—and both compartments are filled with water. In order to make accurate readings the observations must be made in a dark room or closet, using no other illumination than that afforded by a lamp or candle. The red glass wedge is then moved in

[1] In reality this represents a dilution of 1 : 101, but, as allowance is made in the graduated tube for this error, it is a matter of no practical importance.

one direction or the reverse until the two fluids show an equal intensity of red color. The number indicated on the scale, read off at M (see Fig. 214), is the percentage of hemoglobin. As soon as the automatic capillary pipet is emptied into the chamber a and rinsed free of the adhering blood, it should be placed in water or in a one per cent. solution of carbonate of sodium, and should never be permitted to dry until it has been thoroughly cleansed. Immediately after completing the observation the mixing cell G is thoroughly washed and dried; the capillary pipet is also cleansed by repeated washing in the alkaline solution, followed by water, or in water alone. It is then dried by passing a thread of cotton, silk, or floss through the capillary tube; a threaded needle is sometimes advised for this purpose, but chipping of the wall of the tube may result from slight carelessness in introducing the needle, and a hair doubled on itself answers the same purpose without the danger indicated. The two ends of the hair are passed through the tube, and the resulting loop is used as a carrier for the thread, which completes the cleaning and drying. The beginner should see that the instrument is clean before the various parts are put away; the experienced worker is fully aware of the difficulty encountered in cleaning a dried pipet, and therefore does not need the precautionary advice given to the novice.

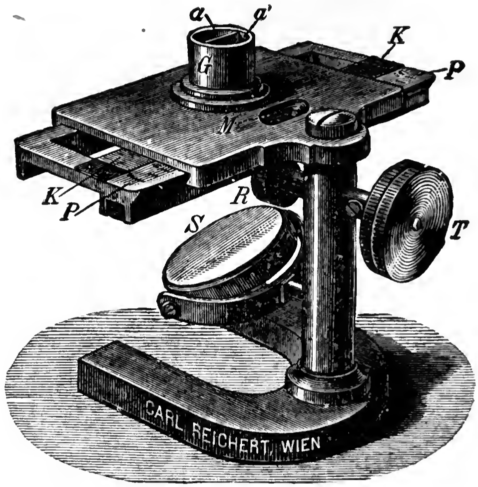


FIG. 214.—VON FLEISCHL'S HEMOGLOBINOMETER.

G. Mixing cell, divided by a partition into two chambers, *a* and *a'*. The blood and water are placed in *a*: *a'* receives water alone, and is directly over the colored glass wedge. *K*, *K*. Glass wedge. *M*. Point at which reading is taken. *T*. Milled head, which moves the head *R*, which, in turn, moves the carriage *P*, *P*, carrying the tinted glass wedge. *S*. Disc of plaster-of-Paris for reflecting the light upward through the glass wedge and the mixing chamber.

The mixing pipet of each instrument is adapted to *that instrument only*, and bears its capacity stamped upon the handle. A similar marking is made on the screw-head at the back of the stage, and as all parts of the instrument are, or should be, numbered, mixing of different pieces should not occur. In order to avoid confusion or incorrect reading where a number of instruments are in use, and when ordering new pipets, this fact must be remembered.

Miescher's modification of this instrument is, in the hands of an expert, more accurate than the original, but is more complicated and costly. The chief points of difference are the use of two mixing cells differing in capacity, each with a projecting partition which receives a grooved cover-glass, and a special mixing pipet for the blood.

Oliver's hemoglobinometer consists of: (1) The automatic blood pipet (Fig. 215, *c*), which has a capacity of five cubic millimeters and

fills readily by capillary attraction. It differs from the fragile capillary measurer that accompanies von Fleischl's instrument in being made of stout glass, and is, therefore, more serviceable. The bore is

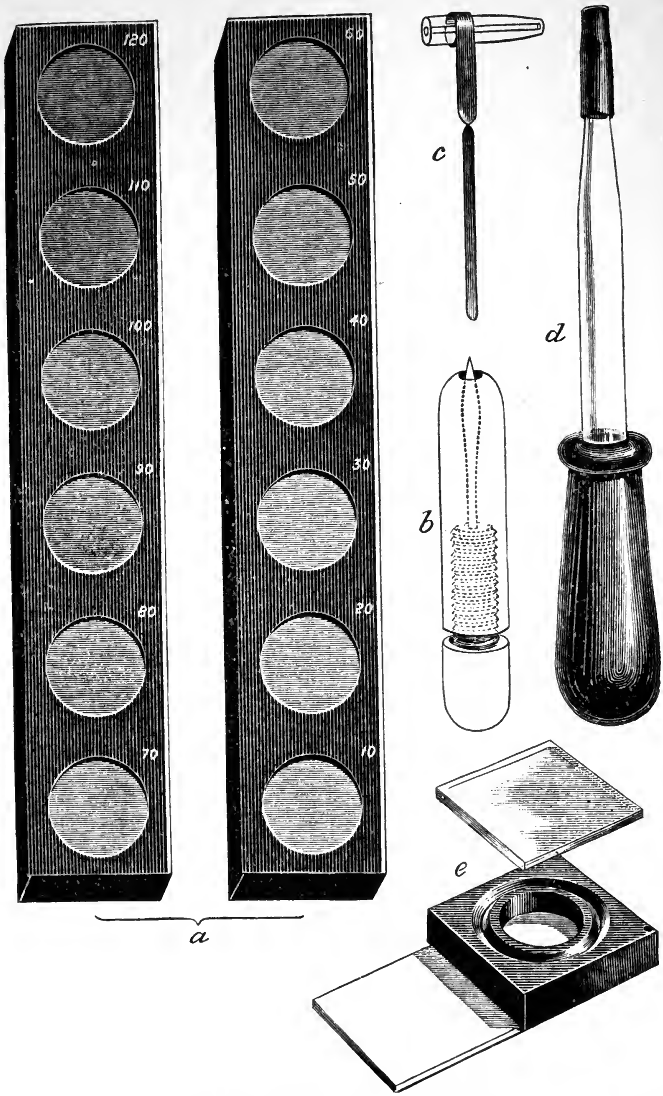


FIG. 215.—OLIVER'S HEMOGLOBINOMETER.
. Standard gradations *b*. Lancet. *c*. Capillary measuring-pipet. *d*. Mixing pipet. *e*. Blood-cell and cover-glass.

dried before an observation by passing through it a needle, threaded with darning cotton. The handle is useful for stirring together the blood and water in the blood-cell. (2) The mixing pipet is provided

with a rubber nozle that fits over the polished end of the blood-measurer and insures complete rinsing out of the blood with the first few drops of water. (3) The blood-cell is of a capacity more than sufficient to insure the complete liberation of the hemoglobin. It yields a blood solution of rather less than one per cent. when filled level with the rim. It is itself the measure of the amount of water to be added, and may be easily and accurately filled. (4) The standard gradations are arranged as circular discs in two slabs—six in each; they represent the divisions of ten degrees of the scale from 10 to 120 inclusive. (5) The riders are small squares of tinted glass provided for reading the degrees intervening between each of the standard gradations. When they are used, the slip of colorless glass is placed over the cover of the blood-cell, so as to balance the effect of the layer of glass in the rider, which is laid over the standard. Two sets of riders have been arranged: one suitable for physiologic observation, to insure the finer readings,—*e. g.*, of one degree,—and the other, sufficient for ordinary clinical observation, to enable the observer to determine differences of 2.5 degrees. For the reading of units, nine riders are required, which are grouped into three slides. It should be premised that the value of the riders is the same neither in the two standards required for candle-light and daylight nor in the upper and lower halves of either standard. This want of uniformity arises from the differences of the specific color-curves in the two standards, and in the two portions of each. In the six lower grades of both standards the value of each rider is double that in the upper six gradations. In the transition grades—the lowermost of the upper half and the uppermost of the lower half—this rule does not accurately apply, but inasmuch as the departure is constant in all observations, and is, moreover, slight, it may be disregarded for the sake of simplicity in using the riders.

The daylight standard is less adapted to the finer readings than that used by candle-light. For the ordinary reading one rider is used: namely, that which is equivalent to five degrees in each slab of the standards. Therefore each set of six standard gradations, whether for candle-light or daylight, has its own rider. When the blood solution is deeper in color than any particular standard gradation, but is overstepped by the rider, the mean between the two may be taken as the reading; and the same rule will apply when the color of the blood is higher than the rider, but is not so high as that of the next standard grade above. Hence, this single rider may be made to provide readings of 0.25 and 0.75. (6) The camera tube: A tube of simple construction is provided, which, being collapsible, will pack into a small compass with the other parts of the apparatus. (7) The light: For observation by artificial light it has been found that the small-sized wax candles known as Christmas candles are the most satisfactory in affording a suitable intensity of light, and a light, moreover, that is sufficiently uniform. The position of the candle is important. It should be such as to shed an equal light on the blood-cell and the standard, and also such as to furnish a high light, so that the flame should be three or four inches above the cells. The distance must be regulated by the observer, who soon learns how to adjust it to the best advantage, so that he may watch the colors with the greatest certainty and accuracy. The actual distance does not affect the reading; but

when the candle is placed too near the points of observation, the illumination becomes too strong, and is somewhat distracting, especially when the lower grades are under observation, these requiring less light.

To Use the Instrument.—The bore of the blood-measurer is first of all dried out by passing through it a needle threaded with darning cotton, and then the polished point is presented to the drop of flowing blood, obtained as directed for other instruments (p. 385). Care must be taken that the pipet is really quite filled; and if it has been necessary to re-apply it to the drop, it should be observed whether there is a break in the column of blood. Any blood adhering to either end must be carefully wiped away with the finger. The rubber nozzle of the mixing pipet, charged with water, is adjusted over the polished end of the measuring pipet, and the blood is washed into the blood-cell by pressing the water through, drop by drop. The handle of the pipet is then used as a stirrer, and the further additions of water are made to impinge on it, as it serves to graduate the size of the drops required accurately to fill the cell. It is easy to do this when the observer catches the reflection of a window on the surface of the fluid. A final thorough mixing with the handle will be required, and perhaps another slight addition of water may be necessary to secure a level filling. The cover-glass is then adjusted, when a small bubble should form—a sure sign that the cell has not been overfilled. If candle-light is to be used, the instrument must be removed to a darkened room, as already directed for von Fleischl's instrument (p. 390). The blood-cell is then placed by the side of the standard gradations, and the eye quickly recognizes its approximate position on the scale. Then the camera tube will more accurately define it. If it is found that the blood solution is matched in depth of color by one of the standard grades, the observation is at an end; but if it is observed to be higher than one gradation, but lower than that above it, the blood-cell is placed

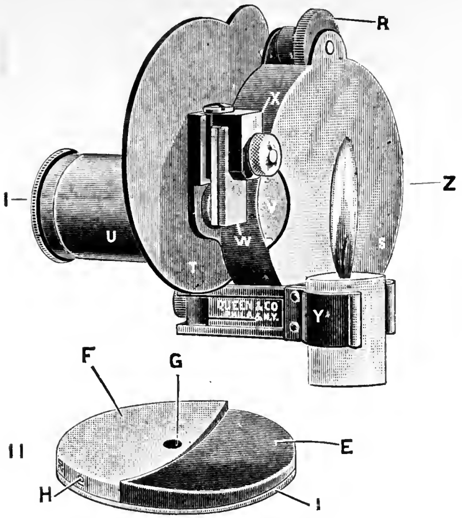


FIG. 216.—DARE'S HEMOGLOBINOMETER.

(Parts assembled as when in use. About one-half actual size.

I.—R. Milled head, which rotates a rubber-covered cylinder that, in turn, acts upon the color-comparison prism V. S. The metallic case containing the color-comparison disc, V. T. The metallic wing that receives the telescoping camera tube U, and, when not in use, rotates eccentrically into place over the back of the metallic box S. U. Telescoping camera tube. V. Visible portion of the disc that carries the color-comparison prism. The space indicated is secured by cutting out a semicircular piece of the metallic front, S. Through this opening the light passes to the color-comparison prism. W. White glass of the pipet. X. Pipet clamp. Y. Spring clamp candle-holder. The leader from Z indicates the point on the side of the metal case, S, where the graduation on the disc, V, is visible, and where the reading is taken.

II.—*Disc Carrying the Color-comparison Prism.* E. Prism of colored glass. F. Semicircle of white glass, upon the edge of which, at H, is etched the graduation. I. White glass backing the color-comparison prism, E. G. Opening through center of disc to receive the pivot of the casing, which acts as a hub around which the disc is rotated.

opposite to the former, and the riders are added to complete the estimation. After completing the observation the same care is requisite in cleaning the instrument as already advised when considering the von Fleischl hemoglobinometer.

Dare's Hemoglobinometer.—In this instrument the undiluted blood in a very thin layer, is compared with a glass color-comparison prism The principle involved is in some respects like that utilized in the von Fleischl instrument, but differs in the fact that pure blood is used. The accompanying illustrations (Figs. 216 and 217) explain the different parts of the instrument.

To Make the Observation.—Before drawing the blood the instrument should be prepared for immediate observation by swinging the screen (T, Fig. 216) outward and attaching the camera tube (U, Fig. 216) and candle-holder (Y, Fig. 216). The candle should be pressed into the holder at such a level that the wax at the wick-end will be on a level with the top of the spring clamp that holds the candle; any curve in the candle-wick should be so turned that its convexity faces the instrument, and the flame should be in line with the metal shank in which the spring clamps are attached, so that the intensity of the candle-light will be equally divided on both the blood and color-comparison sides. As the comparison should be made as soon as possible after the blood has been drawn, a means of lighting the candle should also be at hand. The pipet for collecting the blood (II, Fig. 216, X W; Fig. 217, II) is removed from the tongue in which it fits; the milled head controlling the screw that holds the two pieces of glass (A, B, Fig. 217, II) is turned far enough to release the glass plates; these are separated, cleaned with alcohol, and polished. It is important that they should be free from all foreign substances, and, above all, that they should not be greasy. After thorough cleansing they are returned to their proper position in the following manner: The observer will have noticed that one of the glasses (the white glass) has cemented upon it a thin plate of glass, which extends to within seven millimeters of one end. If the second glass be laid upon the thin plate, a space is formed at one end of, and between, the two glass plates. This is the capillary space, into which the blood is to be received; it is shown at D, figure 217. The glass plates are placed in the clamp with the end containing the space projecting outward, and are secured in this position by tight-

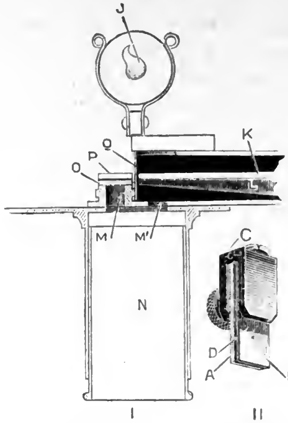


Fig. 217.—Dare's Hemoglobinometer

I.—*Horizontal Section, Viewed from Above* J. Candle in spring clamp. K. White glass on the back of the prism. L. The colored prism used for comparison with the blood, and shown at E in figure 216. M. The opening through which the blood is viewed. M′. The opening through which the comparison color is visible. N. The telescoping camera tube, through which the two apertures, M′ and M, are viewed in making the comparison. O. Transparent glass of the pipet. P. White glass of the pipet. Between the transparent glass, O, and the white glass, P, is the capillary space containing the blood. Q. Metal septum interposed between the blood pipet and the comparison color.

II.—*Automatic Pipet.*—A. White glass. B. Clear glass. C. Pipet clamp in which at C′ is a groove into which the tongue on the stage slides. D Capillary chamber or pipet for receiving the blood. To the left and slightly behind is shown a milled head controlling the screw that clamps the glasses.

ening the retaining screw by means of the milled head. The white glass should be on the side next to the milled head. The clamp with the two glass slips is as shown at II, figure 217. The instrument is now ready for use.

The finger-tip or the lobe of the ear is prepared in the usual way, and the blood is drawn as already directed (p. 385). The free end of the glass slips (A, Fig. 217, II) is now presented to the drop of blood, which at once enters and fills the capillary space, D, figure 217. If the instrument has been properly cleansed, the pipet at once fills to all its margins. Care must be taken to prevent the blood from flowing over the glasses, but in case such an accident occurs, the excess of blood can be readily wiped off. The clamp is at once placed in position, as shown at X, figure 216. When properly placed, the projecting glasses, with their intervening capillary space filled with blood, rest over the opening shown at M in figure 217. In this same sectional view the glasses are shown at O, P; the white glass is at P, the clear glass at O, and between them is the blood. Light the candle, which has already been placed in its proper position. The eye is placed to the drawn-out telescoping tube (U, Fig. 216; N, Fig. 217; in both instances the eye occupies the position of the Roman numeral I in the illustrations), and the line of vision is directed toward a dark surface, with no intervening light, either direct or reflected, except that afforded by the lighted candle. Absolute darkness, such as is necessary for the von Fleischl instrument, is not required. A dark room is to be preferred; bright light is, of course, to be excluded, and the direction of the line of vision should at least be toward a lusterless black surface, such as is ordinarily afforded by a black coat. Looking through the tube N, figure 217 (the instrument being held as shown in Fig. 217, in which case the eye would be at I), the observer sees at the bottom of the tube two apertures (M and M′, Fig. 216), through each of which a more or less faint red or reddish-yellow light is seen. By referring to the diagram, figure 217, it will be apparent that the light coming from the candle, J, passes through the blood between the glasses, P and O, and is visible at M. Other rays of light, starting from the same point, pass through the glass comparison prism L, and are to be seen at M′. The two apertures, M and M′, are closely approximated; the milled head R (Fig. 216) is now turned one way or the other until the light passing through the glass comparison prism and visible at M′ is of the same color as the light coming through the blood and presenting at M. During all the manipulation the graduation has not been seen, unless the observer went out of his way to examine it; when the two colors have been matched, the reading is made on the side of the instrument, just behind the leader from the letter Z. The graduation, as in the other hemoglobinometers, is in percentage of the normal; its location on the disc is indicated at H, figure 216, II. The reading should be made at once on filling the pipet, as after a few minutes contraction and shrinking of the clot occur, giving rise to a marginal illumination with concentration of the colored elements near the center, and thereby offering certain possibilities of error.

When the observation is completed, the clamp X, figure 216, is removed, and the milled head is turned just enough to release the two glass slides, which are separated and at once cleaned. The ease

with which the only part soiled is cleansed contrasts with the great difficulty ordinarily attending efforts satisfactorily to clean the automatic pipets and mixing chambers of the instruments devised by von Fleischl and Oliver.

Estimation of the Quantity of Hemoglobin by the Specific Gravity.—As a rule, the specific gravity of the blood indicates with a fair degree of accuracy the quantity of hemoglobin present, and hence may be utilized as one of the methods for hemoglobin estimation. As alteration in the density of the plasma can not be ignored, and as possible hydremia can not be overlooked, the specific gravity method will always be open to sources of error. In diabetes the evident high specific gravity (not uncommonly 1060 or over) would be misleading; under such conditions the method is not applicable. Influences increasing the density of the blood by abstracting the water, thereby raising the plasmatic specific gravity, vitiate the results obtained by this method. The following table, from Hammerschlag, gives the hemoglobin value of specific gravities between 1033 and 1060:

Specific Gravity.	*Hemoglobin.*	*Specific Gravity.*	*Hemoglobin*
1033–1035	25–30 per cent.	1048–1050	55–65 per cent.
1035–1038	30–35 "	1050–1053	65–70 "
1038–1040	35–40 "	1053–1055	70–75 "
1040–1045	40–45 "	1055–1057	75–85 "
1045–1048	45–55 "	1057–1060	85–95 "

To Determine the Specific Gravity.—The simplest procedure for determining the specific gravity of the blood is the benzol-chloroform method of Hammerschlag. Chloroform possesses a specific gravity much higher than blood (1525), benzol much lower (0889), and as the two fluids are miscible in all proportions, any intermediate specific gravity is readily obtained. The instruments needed are a urinometer or hydrometer jar and an accurate urinometer, the scale of which should reach at least 1060. A mixture of chloroform and benzol is made having a specific gravity of about 1060; the blood is obtained in the usual manner and is drawn into a capillary tube, such as the Thoma-Zeiss pipet or Gowers' pipet, or similar tube; care must be taken that no air is permitted to enter the column of blood. From the pipet a drop is gently and slowly ejected into the chloroform-benzol mixture, being careful to exclude air. If the hydrometer jar, containing the chloroform-benzol mixture, has been properly cleansed and dried, the drop of blood will not adhere to its wall. The blood, not being miscible with the reagents, forms a drop, which floats on the surface of the fluid. Benzol is added, with careful, repeated stirring; the addition is continued until a density is reached in which the drop neither rises to the top nor sinks to the bottom; in other words, the specific gravity of the fluid is made the same as the specific gravity of the drop of blood. The specific gravity of the fluid is now taken, and the result obtained is, of course, the specific gravity of the blood. From this specific gravity the percentage of hemoglobin may be calculated.

Tallqvist's Hemoglobin Scale.—A very simple, but only approximately accurate, method of estimating the hemoglobin is furnished by this device, the essential features of which are a color scale forming one leaf of a book, the remaining leaves being absorbent paper. A

small square of the latter is touched to a blood-drop and the resulting spot compared with the scale.

Remarks on Hemoglobin Methods.—Of the various methods given, that devised by von Fleischl has received most general acceptance. It is said that the von Fleischl instrument is unreliable for very low percentages of hemoglobin; the source of error is best met by using two measures of the blood, secured by filling two pipets and emptying both into the mixing chamber. The resulting reading is halved. Yarrow and Hitchens[1] have compared results obtained by the specific gravity method, by Gowers', von Fleischl's, and Oliver's instruments, and by the hematoscope of Henocque, and after an exhaustive investigation these authors conclude that the instrument of Oliver is by far the most accurate. Next to this method they prefer calculations based upon the specific gravity, and look upon von Fleischl's and Gowers' instruments as constantly liable to error. Dare's instrument, because of the ease with which it is operated and cleaned, the lack of possible error by diluting the blood, and high degree of accuracy, is one of the most satisfactory of the hemoglobinometers now available for general use. The author is impressed by the fact that two individuals can read so close together, variations of two, three, four, and five per cent. being infrequent. The same workers will, in reading the von Fleischl and Oliver instruments, differ to the extent of from five to ten per cent. For physicians to whom one of the more accurate but expensive instruments is not accessible Tallqvist's scale furnishes valuable information. The cost is merely nominal.

The term **percentage of hemoglobin** means the percentage of the normal. If the reading is 100, the hemoglobin is normal; if, however, the reading is 80, there is eighty per cent. of the normal, or twenty per cent. less than normal; if the reading is 120, there is twenty per cent. more than in health.

The **color-index** is the relative richness of each erythrocyte in hemoglobin. As previously stated, the percentage of hemoglobin estimated by the instruments commonly at hand is the percentage of the normal. If in a blood examination we find 5,000,000 red blood-cells and 100 per cent. of hemoglobin, it is evident that both the erythrocytes and the hemoglobin are normal, and the color-index is 1. If, however, the blood contain 2,500,000 red blood-cells and 50 per cent. of hemoglobin, it is evident that, while there is a great reduction in red blood-cells, there is also a proportionate reduction in hemoglobin; it is thus seen that the corpuscular richness of the cells present is the same as in health, therefore the color-index is normal—1. If, on the other hand, as in chlorosis, 4,000,000 red blood-cells are present (assuming as before, for convenience in calculation, that the normal is 5,000,000), then the number of erythrocytes present is 80 per cent. of the normal. If the blood shows the presence of 50 per cent. of the normal amount of hemoglobin, it is evident that the hemoglobin is much more reduced than the erythrocytes; in other words, the color-index is low. The exact color-index is obtained by dividing the percentage of hemoglobin by the percentage of erythrocytes: in the instance given, $\frac{50}{80}$, or $\frac{5}{8}$ (or, in decimals, 0.625), would be the color-index. From the foregoing it

[1] "University Medical Magazine," October, 1899.

will be seen that the color-index may be worked out by the following formula:

$$\frac{\text{Percentage of hemoglobin}}{\text{Percentage of erythrocytes}} = \text{Color-index.}$$

COUNTING BLOOD-CELLS.

The Red Cells.—*The Thoma-Zeiss Hemocytometer.*—This apparatus consists of:

1. A capillary tube of glass, about fifteen centimeters long, expanding in the upper portion into a bulb, in which lies a small glass ball (Fig. 219). The lower portion of the tube is graduated in tenths, from 0.1 to 1, while just above the mixing chamber is the mark 101, indicating that, if filled with blood to the mark 1, and then with some other fluid to 101, the fluid above the point 1 will represent a dilution of 1 part in 100.

2. A counting chamber, composed of a heavy glass slide, the center of which is formed into a circular cell by a rim of glass; in the middle

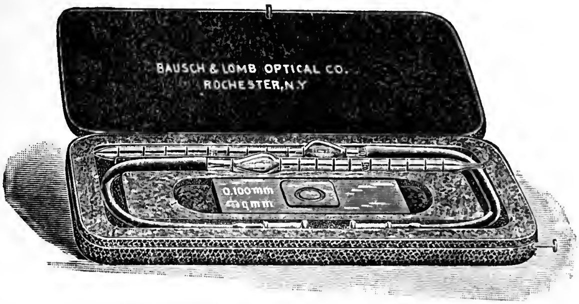


FIG. 218.—THOMA-ZEISS HEMOCYTOMETER.

As shown in the illustration, the different parts are packed in a velvet-lined case for safe transportation. In the center of the case is a glass slide, which contains the counting chamber. As illustrated, the two pipets—one for the erythrocytes and one for the leukocytes—are contained in the single case. The receptacle for thick covers is just under the center of the slide.

of the cell is a circular glass platform. (See A and C, Fig. 221.) When a cover-glass is placed over the cell, the space between the cover-glass and the surface of the counting platform is 0.1 mm. The counting platform has on the center a space ruled in squares, the side of each square being $\frac{1}{20}$ of a millimeter. The cubic capacity, then, of the space surrounded by each ruling and covered by the cover-glass is equal to $\frac{1}{20}$ mm. $\times \frac{1}{20}$ mm. $\times \frac{1}{10}$ mm., or $\frac{1}{4000}$ of a cubic millimeter. The small moat between the platform and the rim receives the overflow of fluid.

A puncture is made in the finger or in the lobe of the ear, as already directed, and the blood is sucked into the capillary tube until it reaches the mark 0.5; after wiping the end of the tube in order to remove the excess of blood, a three per cent. salt solution, or other acceptable diluting fluid, is drawn into the tube until the fluid has risen to the point marked 101, giving a dilution of 1 to 200. This is preferable to using the mark 1 for the blood, with a consequent dilution of 1 to 100 as it avoids the danger of drawing the blood into the bulb of the pipet. In

order to secure absolute control of the blood and diluting fluid, Galli[1] has devised the mixing tube shown in Fig. 220. The vacuum causing the blood to enter the pipet is produced by turning the screw (*f*). To aspirate the diluting fluid more rapidly, the sliding jacket carrying the piston (*d*) is elevated as shown in the small figure. This instrument, while unquestionably permitting a greater degree of accuracy than does the Thoma-Zeiss, would appear to be less readily manipulated. The contents of the tube being thoroughly mixed by shaking, the fluid below the bulb is then expelled, the point of the tube is wiped, and a drop of the diluted blood is placed on the ruled platform of the counting chamber; a cover-glass is then cautiously laid upon the drop, care being taken that the cover does not slip to either side. If a globule of air forms between the cover and the counting platform, the cell and cover should be cleaned and the attempt should be repeated, the cover-glass being so adjusted that no air-bubbles are present. The preparation should be rejected if the liquid makes its way between the cover-glass and the external rim. The cover-glasses used in ordinary microscopy are not suited for use with this instrument; they are rarely flat, cup easily, and in either case may give misleading results. Only the heavy covers that accompany the instrument should be used. The thick cover-glass and the depth of the cell preclude the use of high-power lenses; the most convenient lens for the count is a $\frac{1}{4}$-inch objective, but a $\frac{1}{5}$-inch or $\frac{1}{6}$-inch, with good working distance, may be employed. When purchasing a microscope, the buyer should specify that the medium power objective possess sufficient working distance—space between lense and top of cover-glass—for this purpose. The microscope is so adjusted that the stage is perfectly level. The slide is placed upon the stage and the ruled areas are found and centered by the use of a 1-inch or a $\frac{2}{3}$-inch objective. The medium power ($\frac{1}{4}$-inch objective) is now thrown in the optic axis of the instrument, and, without looking through the eye-piece, the objective is racked downward until it almost touches the cover-glass. The eye is then placed at the eye-piece and the illumination is perfected, after which an accurate focus is secured by slowly focusing upward. At first the corpuscles may be in different focal planes, and it is therefore best to allow the instrument to remain quiet for a few minutes until the cells have been deposited upon the counting platform. The cells should be evenly distributed, as shown at B in figure 221. If they are clumped and not uniformly distributed over the counting platform, the mixing has been inefficient, and the mixing tube must be cleaned and the whole process repeated. Count

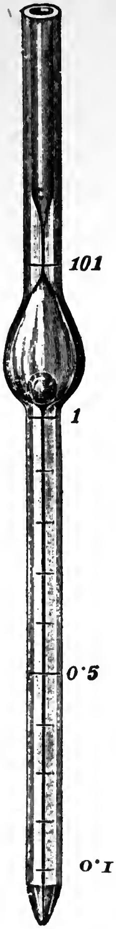


FIG. 219. — CAPILLARY MIXING TUBE OF THE THOMA-ZEISS APPARATUS.—(*Jaksch.*)

[1] "Münch. med. Woch.," 51, No. 13, March 29, 1904.

the corpuscles in at least 80 squares, using 5 blocks of 16 each contained within double lines; these blocks should be selected from various parts of the ruled area in order most nearly to obtain a mean of the entire specimen. Clean the counting chamber, place in it a fresh drop of the diluted blood, and repeat the count, using the average of the two in computing the total. These two counts will, in normal blood, yield about 1000 cells, a number guaranteeing sufficient accuracy. To obtain the total, multiply the number of cells counted by the degree of dilution and by 4000 ($\frac{1}{4000}$ c.mm. being the contents overlying a square), and divide by the number of squares counted. Example: A count gives 490 red cells in 80 squares; $\frac{490 \times 200 \times 4000}{80} = 4{,}900{,}000$,

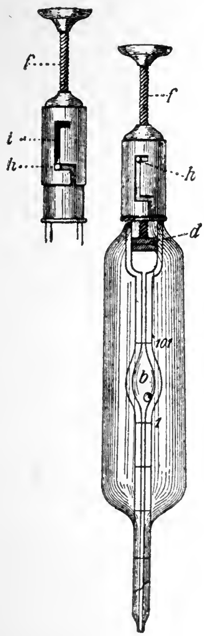


FIG. 220.—MIXING TUBE OF GALLI.

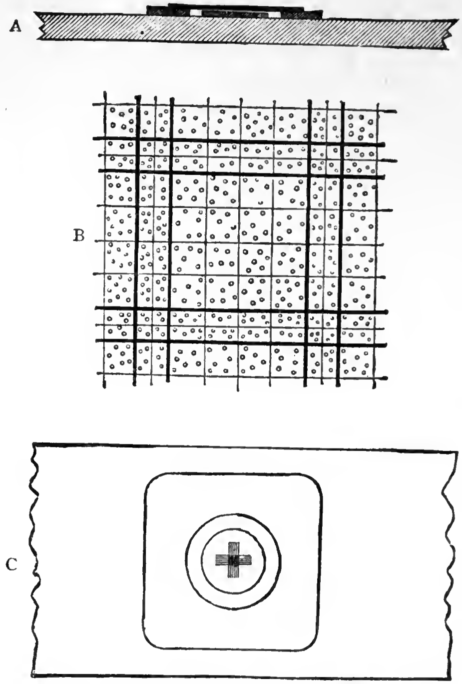


FIG. 221.—COUNTING CHAMBER OF THE THOMA-ZEISS HEMOCYTOMETER.—(*Landois.*)

A. Sectional view. On the upper surface is shown cover-glass in position. Beneath the center of the cover is a glass platform, upon which is ruled the divisions shown in the surface view, C. The space between the cover and the ruled platform is 0.1 mm. On each side of the ruled platform is shown the moat that prevents the fluid from reaching the outer disc, upon which the cover-glass rests. B. Appearance of the ruled surface under microscope and showing uniform distribution of the red cells as they should appear in a properly prepared dilution.

the number of cells in one cubic millimeter of blood. It will readily be seen that if 490, the number of cells counted, be eliminated from this formula, the remaining numbers, 200 × 400 ÷ 80, will give 10,000. Hence if this degree of dilution and number of squares be employed in each count, the problem is reduced to multiplying the number of cells counted by 10,000; this is simply annexing four ciphers, and the total is thus obtained instantly without computation. In recording the corpuscular richness (erythrocytes or leukocytes) of the blood

it is customary to give simply the number without stating the quantity of blood—*e. g.*, "4,900,000 red cells" means that that number was found in one cubic millimeter of blood.

Counting White Corpuscles.—To count the white corpuscles in a dilution such as that used for the red would require more time and a much larger ruled space than is available in the Thoma-Zeiss instrument. For this reason a lower dilution is used,—1:20, instead of 1:200,—and, for diluting, a 0.33 per cent. solution of acetic acid, which destroys the red blood-cells, at the same time making the white cells more distinct. The entire field of 400 squares should be counted in at least two, and better three or four, drops. The method, with the foregoing exceptions, is as given for the red; in the calculation, 20 is substituted for 200 and 400 for 80. The constant factor in such formula will be 200, and this may be used for multiplying the number of leukocytes counted, in the manner that 10,000 is employed for the red cells. Better than the Thoma-Zeiss chamber for counting the leukocytes, however, is the Zappert, or, if preferred, one of the many still more elaborately ruled stages, in which eight additional large squares surrounding the one representing the older pattern are made available. Counting the entire nine squares, gives the equivalent of 3600 of the small squares, and one filling of the counting chamber suffices. With such a chamber the leukocytes may be counted in the mixture employed for enumerating the red cells if either of the following diluting solutions be used:

Toisson's Solution.

Methyl-violet,	0.025	gm.
Sodium chlorid,	1.0	"
Sodium sulphate,	8.0	"
Glycerin,	30.0	c.c.
Distilled water,	160.0	"

Sherrington's Solution.

Ehrlich's purified methylene-blue,	0.1	gm.
Sodium chlorid,	1.2	"
Neutral potassium oxalate,	1.2	"
Distilled water,	300.0	"

The anilin dyes contained in these solutions stain the leukocytes, and thereby make possible their enumeration. A stain may also be added to other diluting fluids.

Cleaning the Hemocytometer.—In every instance this should be done as soon as the count is completed. The counting chamber must be cleaned with water only, and this should not be hot; otherwise the cement holding the rim of glass will be softened. Various methods for cleaning the pipets are recommended, most of them making use of water, alcohol, and ether in the order named. The simplest and by far the best plan is to remove the rubber tube and expel the contents of the pipet by means of a small ear syringe fitted over the end. Keeping the bulb compressed, the free end of the pipet is immersed in water and the bulb allowed slowly to expand, thus filling the pipet, which in this manner is washed twice with water and twice with alcohol. It is then dried by warming over a Bunsen burner sufficiently to vaporize the alcohol. This can be done without endangering the instrument if it be kept constantly rotating and is tested by the fingers to guard

against overheating. Vaporization is aided by occasionally forcing air through the pipet with the bulb.

Differential Counting.—Dried and fixed films are stained by Ehrlich's or Wright's stain, and mounted as already directed. Then the leukocytes are counted by traversing, in straight lines, more or less of the stained field, carefully avoiding going over the same point twice and counting at least 500 leukocytes. A mechanical stage greatly facilitates the count. On a piece of paper by the side of the microscope are arranged columns, at the top of which are written the forms of leukocytes; after counting the required number, the columns are added

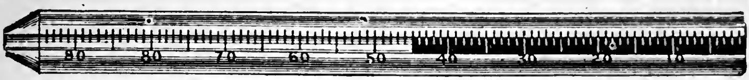


FIG. 222.—HEMATOCRIT TUBE. (Twice natural size.)
The tube as illustrated has been filled with blood and rotated, as directed in the text, until the erythrocytes have collected at one end, occupying 45 degrees (or graduation-marks). This, multiplied by 100,000, gives 4,500,000 —the number of erythrocytes to the cubic millimeter of blood.

and the percentage of each form present is calculated. Differential counting of diseased red cells is sometimes resorted to, and may be done in the same manner.

Hematocrit.—This instrument (see chapter on Examination of the Urine) readily enables one to estimate the *volume of the red corpuscles.* It consists of:

1. Two glass tubes, 50 mm. long, with a lumen of 0.5 mm., and graduated into 100 parts. (Fig. 222.)

2. A metallic frame (Fig. 223), in which the glass tubes are fastened —on the outer side by a metallic cup in the frame, and at the proximal extremity by a spring, which is attached to a hollow metal cylinder,

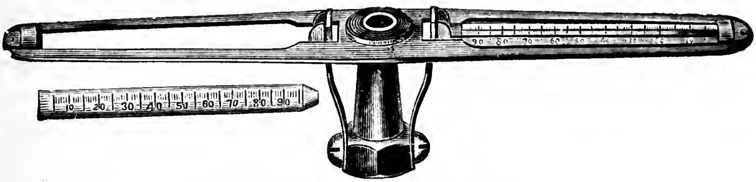


FIG. 223.—ROTATING FRAME OF THE HEMATOCRIT.
The tube on the right is in position; the tube on the left shows the graduation and the direction which the smaller end should take when in position. The entire metal frame is to be placed on the vertical support, as described in the chapter on Examination of the Urine.

which projects downward from the center of the frame, and by means of which the frame can be made to rotate on a vertical axis. The cups receiving the ends of the glass tubes contain rubber washers that also act as cushions.

3. A vertical support, which can be made to rotate. A speed of at least 10,000 rotations a minute is necessary.

4. A metallic box, to be fastened to a table, and containing the machinery by which the vertical support is rotated.

To Use the Hematocrit.—One of the graduated tubes, previously well cleaned, is attached by means of a short piece of pure rubber tubing

to a medicine-dropper. The bulb of the dropper is gently compressed, and the end of the graduated tube is presented to the escaping blood; the compressed bulb of the pipet is slowly released, thereby sucking the blood into the capillary tube. As soon as the tube is full, the end in the drop of blood is pressed against the patient's thumb or other surface from which the blood is being obtained, without withdrawal from the drop, and the rubber tube and the medicine-dropper are detached from the hematocrit tube. Figure 224 and the legend explain the usual method by which the tube is filled. If but one tube is to be filled, the other should be in place in the rotating frame of the instrument, to act as a counterpoise to the charged tube. As soon as the latter is filled, it is placed in position in the frame, which is at once rotated at the rate of 10,000 revolutions a minute for two minutes. The red blood-corpuscles collect in the distal extremity of the tube, the leukocytes near the center, and the liquor sanguinis in the proximal portion. Find the number of degrees the red cells occupy, and, as each degree represents approximately 100,000 cells to the cubic millimeter, the addition of five ciphers gives the number of red cells to the cubic millimeter. Thus, if the red cells occupy fifty graduations on the scale, there are 5,000,000 red cells to the cubic millimeter. (See Fig. 222.)

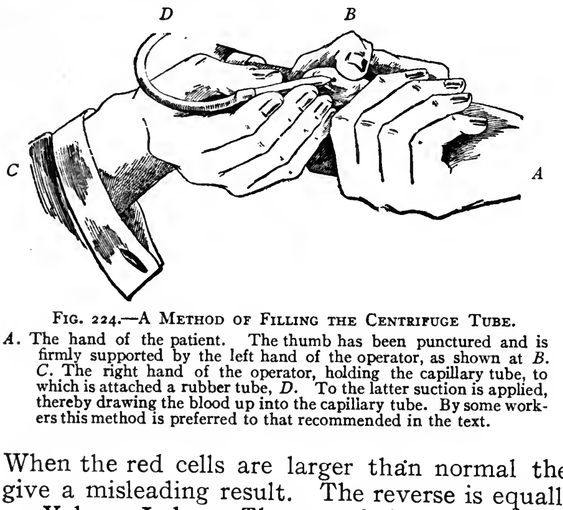


FIG. 224.—A METHOD OF FILLING THE CENTRIFUGE TUBE.

A. The hand of the patient. The thumb has been punctured and is firmly supported by the left hand of the operator, as shown at *B*. *C*. The right hand of the operator, holding the capillary tube, to which is attached a rubber tube, *D*. To the latter suction is applied, thereby drawing the blood up into the capillary tube. By some workers this method is preferred to that recommended in the text.

It is apparent that the result is in volume of red cells, and not the number that must be obtained by a calculation which does not take into consideration the size of the cells. When the red cells are larger than normal the greater volume would give a misleading result. The reverse is equally true.

Volume Index.—The use of the hematocrit in conjunction with the hemocytometer makes possible the determination of the volume index, which indicates the volume of the individual red cell as the color index represents its hemoglobin content. It is obtained by dividing the percentage volume of the red cells by their percentage number. Example: If the column of red cells in the hematocrit reaches 45 instead of 50, the normal, the percentage volume is 90; if the count be 4,000,000, the percentage number is 80; $90 \div 80 = 1.125$, the volume index.

Coagulation Time.—No reasonably satisfactory method for determining the coagulation time of the blood has been devised. The simplest is that of Milian, which consists in placing a large drop of blood upon a clean glass slide, the latter being tilted toward a vertical plane after the lapse of a few minutes to determine if the shape of the drop is thereby changed. During the time it is fluid, this manipulation causes the drop to assume a pear shape; when coagulation has occurred, tilting does not change the outline of the drop. Normally, coagulation

is said to occur in five minutes; personal observations indicate that a considerably longer time is usually required. The **hemogelometer** of Biffi gives promise of being a valuable device. Essentially it is a large glass tube closed by a doubly perforated stopper which transmits a thermometer and a glass rod. From the lower end of the latter projects a platinum wire bearing a series of loops which can be lowered into the water half filling the tube. These loops are in succession touched to drops of blood, and after a few minutes are at regular intervals immersed by lowering the wire. Coagulation is shown when a drop fails rapidly to diffuse in the water, ordinarily in from seven to ten minutes.

Wright's **coagulometer** is one of the more elaborate instruments, but for clinical work is little, if any, better than those named, one of the principal objections being the large quantity of blood required. It consists of a set of heavy glass tubes, with a capillary bore, open at both ends. At intervals of a minute the tubes are partly filled with blood and kept at body-temperature by immersion in water. In succession the blood is forced out upon white paper by blowing into the tubes, coagulation being shown by the presence of a capillary clot. The elapsed time since that particular tube was filled is the coagulation time, which in normal blood is usually from four to seven minutes.

GENERAL PATHOLOGY, COMPOSITION, AND STRUCTURE OF THE BLOOD.

The circulating normal blood consists of a fluid portion (the **liquor sanguinis**) in which are suspended the solid elements—the blood-corpuscles or blood-cells. The liquor sanguinis is probably identical—or practically so, at least—with the circulating medium outside the blood-vessels in the primitive lymph-spaces, which passes to the lymph-nodes and is returned to the circulation. As a part of the blood, the liquor sanguinis is more than a mere vehicle for the transportation of the solid elements, and with its complex chemistry is the essential food-carrying body to the tissue at large. It is composed of the elements out of which serum and fibrin may be formed; and while this separation, so far as the plasma is concerned, is largely a death change, still, evidence is not wanting to show that fibrin formation may be an essential element in the protection of the organism and in repair. Thus, the distinct wall of fibrin that forms around infected areas or covers an infected serous surface, such as a pleura, and through which osmosis and the absorption of bacterial products are reduced to a minimum, acts not only as a scaffold upon which embryonic tissue, and eventually granulation tissue, can build the framework which is to repair the injured part, but also as a prophylactic, limiting membrane, through which infection travels only with the greatest difficulty. Again, of all the structures produced within the body, fibrin offers the greatest resistance to many of the injurious incidents to which the tissues are liable; the constant pressure of the circulating blood, as in an aneurysm, may lead to atrophy and to the disappearance of bone, unless conditions arise that determine the intervention of a wall of fibrin, through which, not uncommonly, we may hope for a cure. The exact factors that enter into the chemistry of fibrin formation are not known; although the third corpuscle (blood-platelet) seems to bear some causative relation to

the process, the character and extent of such influence remain one of the unsolved problems of physiologic chemistry.

An excess of fibrin, or, more truly, of fibrin-forming elements, constitutes **hyperinosis**—a condition present in pregnancy, and occasionally in chlorosis and other forms of anemia. **Hypinosis,** or reduction in the fibrin-forming elements, is sometimes observed in leukemia and pernicious anemia. In addition to the influences modifying the amount of fibrin, there are marked differences in the rapidity with which it is formed. As a rule, intravascular coagulation begins shortly after death. To this, however, there are notable exceptions. The author recalls a case of pernicious anemia in which, at the postmortem, made twelve hours after death, the blood had not coagulated. After removal from the cardiac cavities a quantity collected in a jar for later study developed a satisfactory coagulum. The blood is less coagulable in hemophilia, in which disease its coagulability may be, in some cases, increased by the administration of calcium salts, while in other cases the local application or the internal administration of these agents fails to influence the condition. Lessened coagulability is present in the blood after death from poisoning by carbonic acid or by carbon monoxid and in some cases of asphyxia. Snake-venom and bacterial products lessen the coagulability of the blood.

Hydremia[1] is a condition in which the blood contains an excess of water. After a hemorrhage the volume of blood is made up by the abstraction of fluid from the tissues at large, and consequently there is a more or less temporary hydremia. When it is reasonable to believe that there is an increased amount of blood, and that the increased quantity is due to the addition of water or saline solutions, as after the injection of a large quantity of normal salt solution, the condition is called **hydremic plethora.** Under ordinary conditions hydremia quickly disappears, as a result of the excretion of water by the emunctories, particularly the kidneys.

Anhydremia is the reverse of hydremia. The lessened amount of water present in the blood usually results from its rapid extraction, although it is conceivable that a diminished supply would induce the same condition. The concentration is usually brought about by the discharge of fluid by the skin, intestine, or kidney. As the principal constituent so removed is water, it is this element that is reduced. As a rule, anhydremia, like hydremia, is temporary. In the former condition the tissues quickly supply the requisite amount of fluid.

In a number of morbid conditions the blood-plasma contains abnormal bodies or normal constituents in abnormal quantities. A small quantity of fat is present in normal blood; occasionally, however, as in alcoholism, diabetes, and a few other conditions, it may be markedly increased, producing a condition called **lipemia.** The fat may be recognized in the freshly drawn blood as small, highly refractile granules which not uncommonly manifest active movement. The examination is conducted as already directed. (See p. 244.) Dry spreads fixed in osmic acid (pp. 33 and 34) will show the blackened fat droplets. (See also Demonstration of Fat, p. 244.) The serum obtained by the centrifuge may contain enough fat to render it turbid. The small

[1] See also p. 261.

quantity of glucose normally present in the blood is markedly increased in diabetes, in which disease it may be present to the extent of 0.7 per cent. instead of the normal, 0.117 per cent. An increased amount of sugar in the blood is called **glycemia.** In leukemia, in pneumonia, in some forms of anemia, and at times in Bright's disease there is an increase of uric acid, or, more properly, of uric acid salts, in the blood. In gout the increase in urates (**uratemia**) is sometimes most marked.

The presence of bile pigments in the blood (**cholemia**) is the essential phenomenon of jaundice (p. 234). Clinicians recognize a form of intoxication which has long been termed **uremia.** At one time this was presumed to be due to the presence of an excess of urea in the blood. Later investigations have shown, however, that no quantity of urea, however large, introduced into the circulation reproduces the clinical picture of the uremia. Blood-plasma also contains certain globulicidal bodies destructive to red blood-cells of other animals. The bactericidal and antitoxic bodies in the blood have already been considered. (See pp. 98 to 104.)

Recent investigations, both experimental and clinical, seem to indicate that a study of the freezing-point of the blood may be of value in certain cases. Normal blood freezes at about 0.55° to 0.58° C., below the freezing-point of distilled water. Agents causing renal irritation or necrosis, such as cantharides, and morbid conditions associated with renal insufficiency, may lower the freezing-point to 0.6° or 0.8° C. or even beyond this point. The removal of one kidney similarly influences the freezing-point.

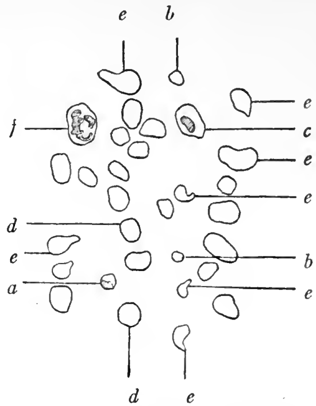


FIG. 225.—DIAGRAMMATIC REPRESENTATION OF VARIOUS FORMS AND SIZES OF RED CELLS.—(*From a case of pernicious anemia reported by Dr. J. C. DaCosta, Jr.*)

a. Erythrocyte (introduced to give an approximate idea of the size of other cells). *b, b.* Microcyte. *c.* Megaloblast. *d, d.* Macrocyte (larger macrocytes are also outlined, some of which are poikilocytes). *e, e, e, e, e, e.* Poikilocytes; other poikilocytes are also shown. *f.* Finely granular oxyphile (polymorphonuclear leukocyte). The granules are not shown, but the extreme irregularity of the nucleus is indicated.

The chief solid constituents of the blood are the red corpuscle, or erythrocyte; the white corpuscle, or leukocyte; and the blood-platelet.

The red blood-cell, or **erythrocyte,** of man is a smooth, highly elastic, biconcave disc, which does not possess a nucleus. From seventy to eighty per cent. of the erythrocytes possess an average diameter of 7.5 μ. Of the remaining twenty per cent. about half are slightly larger, and the remaining cells slightly smaller, than the average given. In the normal blood, cells smaller than usual are probably more frequent than the larger cells. The smaller cells usually measure between 6 μ and 7 μ, although cells measuring less than 4 μ (dwarf cells) may occasionally be observed. The larger cells are more conspicuous in infancy, and are rarely seen after adolescence. In a number of morbid processes abnormal form and size constitute important alterations. In certain anemias many of the cells are small (**microcytes**); the condition is called **microcytosis,** or **microcythemia.** In some instances a vary-

ing number of the erythrocytes possess diameters of 8 μ or 9 μ, or are even larger; an occasional cell may attain a maximum measurement of 15 μ. Such cells are called **macrocytes,** or **megalocytes,** and the condition is known as **macrocytosis,** or **macrocythemia.** Microcytes are not uncommonly spheric, and in macrocytes the biconcavity is often inconspicuous or absent. Microcytosis and macrocytosis are frequently associated. The small hemal element described by Eichhorst is really an irregularly staining microcyte from 2.5 μ to 4 μ in diameter. It differs from the usual microcyte in the intensity with which it stains.

As a result of disease, erythrocytes may change their form, becoming ovoid, pyriform, knobbed, bobbin-shaped, etc. Cells showing such abnormality in form are called **poikilocytes,** or **schistocytes;** the condition is known as **poikilocytosis.** Microcytes and macrocytes, as well as the nucleated forms to be considered later, not uncommonly manifest more or less irregularity in shape, and may be properly considered as poikilocytes. It is possible, by error in technic, to produce a distortion of the erythrocytes, which may mislead the uninitiated. If, in making the cover-glass spreads, as already directed, the two cover-glasses (p. 385) be left in contact too long, the act of separation may stretch the erythrocytes so that one diameter will be greater than

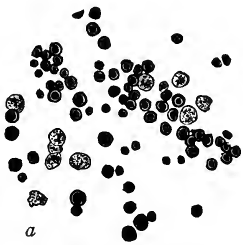


FIG. 226.—TYPES OF RED BLOOD-CELLS; ALSO LEUKOCYTES, AS AT *a*.—(*Landois.*)

FIG. 227.—POIKILOCYTES.

another, a condition frequently observed in poikilocytosis. A careful study of such a field will show that the cellular distortion leads to an elongation of all the affected cells in one direction, a condition never observed in true poikilocytosis.

Crenation is an appearance closely resembling poikilocytosis, but develops after the blood has been drawn. Crenated cells are irregular, and show knobbed projections from their surfaces associated with more or less shrinking of the protoplasm; by some it is believed that crenation is the extravascular analogue of intravascular poikilocytosis.

Early in fetal life the **nucleated red blood-cells** normally present at that period begin to disappear, and at birth, or shortly after, are no longer present in the normal blood. In certain morbid conditions, however, they form conspicuous hemal elements. It is usually held that at some stage in its evolution the red blood-corpuscle possesses a nucleus, which disappears before the cell assumes the function of a hemal cell. Exactly how this disappearance of the nucleus is accomplished has not been accurately determined. According to some observers, the nucleus disappears by extrusion, while others think it is removed by a process of absorption or of disintegration. The nucleated

cells seen in the blood are of different sizes, justifying to a certain extent the division into three kinds.

Normoblasts are nucleated red cells the diameter of which is approximately that of the normal erythrocyte. The size of the nucleus varies, and it is usually eccentric in location. It is rich in chromatin, stains with intensity by the usual nuclear stains, and not uncommonly contains a fine, intranuclear net. Occasionally, the nucleus will be found partly outside of the protoplasm—a condition that suggests its extrusion. Sometimes, in properly fixed preparations evidences of mitosis may be present, or the cell may contain two or even three nuclei; these may appear distinct and separate, while in other cells connecting bands of chromatin may be recognized. The perinuclear protoplasm contains more or less hemoglobin, and hence stains with the acid anilin dyes. The outline of the cell is commonly uneven, so that a varying percentage of these cells may properly be called nucleated poikilocytes, or **poikiloblasts.**

The **microblast** is a small nucleated form, smaller than the normal red blood-cell; both nucleus and protoplasm are diminished in quantity, although occasionally microcytes may be found possessing a nucleus as large as the nucleus of the normoblast. Intranuclear changes are infrequent. The perinuclear protoplasm is not uncommonly shredded, and the cell is regarded by most observers as a degenerated, necrobiotic, or fragmenting form of the normoblast.

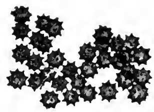


FIG. 228.—CRENATED RED BLOOD-CORPUSCLES. — (*Landois.*)

Often seen in improperly fixed blood slides, in freshly drawn blood after prolonged study under the microscope, in urine, etc.

Megaloblasts, or **macroblasts** (also called *gigantoblasts*), are abnormally large red cells possessing nuclei; the diameter of such cells usually exceeds 10 μ, and may attain 16 μ. The nucleus is relatively large, but stains with less intensity than the nucleus of the normoblast. The perinuclear protoplasm is usually rich in hemoglobin. The cell not uncommonly shows degenerative changes, as indicated by the unevenness in staining and by the occurrence of vacuoles in its interior. Frequently such cells are irregular in conformation, and may be properly called poikiloblasts. The demonstration that unusually large red blood-cells (megalocytes or megaloblasts) may contain more hemoglobin than corpuscles normal in size possibly explains the fact that in certain diseases in which these cells are comparatively abundant the color-index may be high. (See Pernicious Anemia.)

In addition to abnormality in size and shape, certain necrotic alterations are sometimes present in the red blood-cells. By some, poikilocytosis is regarded as an evidence of necrotic change, and the endoglobular alterations about to be described are not uncommonly associated with, or terminate in, the production of poikilocytes. The central normally pale area of the corpuscle may increase in pallor, and may eventually lose all its coloring-matter; the periphery at the same time may show deepening of color. Sometimes hyaline or vacuolated spots appear in the periphery of the cell, or the cell becomes ovoid in profile with a vacuole at one or both ends. A number of these changes, associated with solution of the hemoglobin and other soluble parts of

the cell, have been grouped by Arnold under the name **erythrocytolysis,** or **plasmolysis.** Crenation, which ordinarily is not developed for some time after the blood is drawn, may be present immediately after shedding. The knob-like projections seen on crenated cells may break off (**plasmorrhexis**) and float free in the blood.

Baspohilic granulation of the erythrocyte occurs in various types of anemia, but approaches constancy in only one, that due to chronic lead-poisoning. In cases of this condition presenting an atypic symptom-complex **basophilia** becomes a prominent diagnostic feature. It is present in some cases of pernicious anemia, leukemia, carcinoma, malaria, septicemia, and chronic suppuration. The granules vary in size and may be distributed throughout the cell or grouped in small or large masses; they are well shown by Wright's stain. The older view that the process is a degeneration of the protoplasm of the red cell is still held by many observers, although Nägeli and others consider it regenerative in nature. Vaughan[1] has reached the conclusion that basic-staining granules in small numbers are present in the red cells of healthy persons, and regards them as the fragmented remains of nuclei. This view is in a degree supported by the fact that nucleated reds are usually numerous in the most marked cases of basophilia.

The number of red blood-cells normally present is approximately 5,000,000 in man and from 4,000,000 to 4,500,000 in woman to each cubic millimeter of blood. Blood containing more corpuscles than normal is said to show **polycythemia** (polyglobuly); a reduction in the number of erythrocytes is called **oligocythemia.** Within the first twenty-four hours following birth a maximum of from 6,000,000 to 6,500,000 may be reached. The number is reduced by hemorrhage and by various anemias, which will be considered later. The number is reduced by prolonged exertion, and menstruation usually induces a slight decrease. The most marked diminution in number is seen in pernicious anemià, in which the oligocythemia may be extreme. Counts as low as 500,000 are not infrequent, and a minimum of 143,000 has been recorded.

Aside from the physiologic increase in the number already noted as present for a brief period after birth, little is known of the etiologic factors active in the production of **corpuscular plethora,** or polycythemia. Impeded circulation, or even the influence of gravity, may slightly increase the number of corpuscles present in a given area. In cyanosis and in cardiac lesions associated with peripheral stasis relatively high counts are not infrequent. The polycythemia observed in the cyanosis of congenital heart disease may be extraordinary, as in the case reported by Baunholtzer—9,447,000 erythrocytes, 160 per cent. of hemoglobin. As a result of the loss of fluid from the vascular system,—as by serous diarrhea, profuse sweating, excessive vomiting, etc.,—the temporary concentration of the blood increases the number of corpuscles present in a given quantity. The condition is, as a rule, temporary under such circumstances. An interesting form of polycythemia is that which develops during residence in high altitudes. As a rule, the maximum polycythemia resulting from this cause does not manifest itself for a month or more, but not infrequently within twenty-four hours after the ascent a notable increase in the number of red blood-cells may be observed. Solly records an instance in which a day's excursion was

[1] "Jour. of Med. Research," vol. x, 1903, p. 342.

attended by an increase of 600,000 red cells. The total rise in the number of red cells may reach from twenty to fifty per cent., not infrequently exceeding the latter. The erythrocruorin does not keep pace with the increase in red blood-cells, although the percentage of hemoglobin is usually augmented. Whether the polycythemia is due to increased peripheral distribution, to more active blood production, or to the lengthened life of the red blood-cells has not been satisfactorily determined; the last named is possibly the most important factor. The polycythemias of phosphorus-poisoning, carbon-monoxid-poisoning, and that occasionally observed in tuberculosis have not received any fully satisfactory explanation.

Polycythemia with chronic cyanosis and enlarged spleen,[1] accompanied by vasomotor and other disturbances, form a symptom-complex of which a number of cases are now on record. The red cells usually range between 8,000,000 and 10,000,000, though a count of 12,000,000 has been found; the hemoglobin commonly is from 115 to 160 per cent. with a recorded maximum of 200 per cent. In some instances the cyanosis is violet rather than blue, suggesting an added hyperemia. The disease, if it may be called a clinical entity, is of long duration, four to ten or more years. The lesion of the spleen is commonly a diffuse hyperplasia, though in a few cases the organ was little if any enlarged. Tuberculosis was found in one case, but Osler believes this affection differs from the somewhat similar condition which is found in primary tuberculosis of the spleen. The entire pathology of this form of polycythemia is still uncertain.

Structurally, the red blood-cell appears to be composed of two elements—a delicate reticulum or stroma, but partly soluble in water, inclosing spaces within which lies an albuminous soluble portion of the cell, which contains the hemoglobin. This part is freely soluble in water. **Hemoglobin,** or erythrocruorin, is the soluble pigment to which the color of blood is due. It is a complex proteid, readily decomposable into a number of so-called reduction products. Some of these have been considered with pigments. (See Pigmentary Infiltration, p. 233.) The amount of hemoglobin present in the blood varies within certain limits. It may be said that, approximately, 100 gm. of blood contain 14 gm. of hemoglobin. It will be recalled that in considering the methods of estimating the quantity of hemoglobin the results are commonly given in percentages of the normal. It will, therefore, be apparent that when a hemoglobinometer records 100 per cent., the quantity indicated is 14 gm. in 100 gm. of blood. Hemoglobin combines with oxygen to form oxyhemoglobin, which, when carried to the tissues, yields its oxygen, the hemoglobin remaining as reduced hemoglobin. With CO it forms a more stable compound, called carbon-monoxid-hemoglobin. The carbon monoxid compound is not readily dissociated, and hence in poisoning by carbon monoxid the oxygen-carrying power of the blood is held in abeyance as a result of the inability of the oxygen to displace the more firmly combined gas. Methemoglobin, hematoidin, hemin, and other pigments derived from the blood have been considered with pigments where they possess any pathologic significance, and for further consideration the reader is referred to text-books on physiology. As the amount of hemoglobin present in the cor-

[1] For literature see chapter on Diseases of the Spleen.

puscles largely influences their specific gravity, the latter has been utilized as a method of determining the percentage of hemoglobin present. (See p. 397.)

When the quantity of hemoglobin falls below the normal, the condition is called **oligochromemia.** Hemoglobin is diminished in all anemias, and not uncommonly its diminution is in direct proportion to the reduction in the number of red blood-cells; in other instances the corpuscular richness in hemoglobin may be greatly reduced without any marked reduction in the number of red blood-cells. These alterations in the quantity of hemoglobin present will be considered with more detail when dealing with individual forms of anemia.

Leukocytes.—The white cells of the blood, unlike the red, are found in a number of forms, the relationship of one form to another not having been clearly established. Unlike the red blood-cells, the leukocytes are nucleated, and normally contain no hemoglobin. The proportion of leukocytes to red blood-cells varies widely in health, the variation depending upon the temporary rise and fall in the number of leukocytes, irrespective of coincident changes in the number of erythrocytes. All authors recognize these fluctuations in the number of leukocytes, but all are fairly agreed that the relative proportion of leukocytes to red blood-cells is 1 of the former to 500 or 600 of the latter. The various forms of leukocytes exist in the blood in fairly constant proportions. The different forms, the general descriptions, and the percentages present in the normal blood will be found in the accompanying table. (See pp. 414 and 415.) In addition to the groupings there given, several of which possess only historic interest, it is necessary to recognize that certain cells are essentially hemal and that others are essentially celomic, although each not uncommonly invades the domain of the other. The normal number of leukocytes in a cubic millimeter of blood approximates from 6000 to 9000.

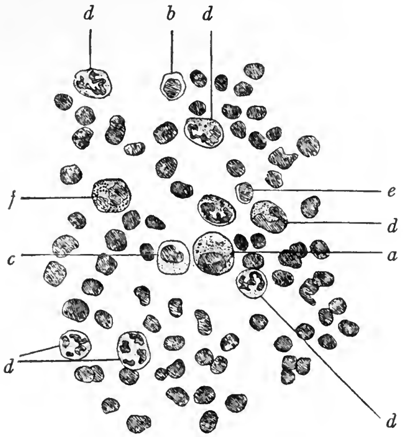


FIG. 229.—DIAGRAMMATIC REPRESENTATION OF LEUKOCYTES.

a, b. Lymphocytes. *c.* Hyaline cell. The cell outlines are not so sharp as indicated. *d, d, d, d, d.* Finely granular oxyphile (polymorphonuclear) leukocytes. *e.* Myelocytes. *f.* Coarsely granular oxyphile (eosinophile) leukocytes.—(*From splenomedullary leukemia; drawn by Dr. J. C. DaCosta, Jr.*) See Figs. 156 and 157, p. 290.

In many conditions a reduction in the number of leukocytes (**hypoleukocytosis, leukopenia,** or **leukocytopenia**) occurs. Such reduction is found with considerable constancy at some period during the course of many of the infectious diseases, particularly typhoid and paratyphoid fevers, measles, influenza, Malta fever, leprosy, malarial fevers, and uncomplicated and advanced tuberculosis. Leukopenia occurs not uncommonly in advanced pernicious anemia, splenic anemia, secondary anemias, and in chronic enteritis of children. This phenomenon is

not a constant feature of any disease. The leukocytes are reduced by starvation, and preliminary to leukocytosis—particularly to that form called inflammatory—a temporary leukopenia is sometimes present. In conditions usually accompanied by an increase in the leukocytes, as appendicitis, peritonitis, and pneumonia, an overwhelming infection may not only prevent an increase but actually cause a decrease in those cells. Under such circumstances, leukopenia possesses the gravest prognostic significance. In marked cases of hypoleukocytosis the number of leukocytes may be 600 or even less to the cubic millimeter of blood. The essential cause of this condition is not known. It is held by some that there is a faulty production of leukocytes; by others, that there is an increased destruction—**leukolysis.** It is not improbable that both factors are operative. Faulty distribution may have something to do with diminution of leukocytes in the peripheral circulation, as indicated by its occurrence after prolonged cold baths and reduction of blood-pressure, the normal distribution being altered as a result of leukocytic accumulation in the large viscera, particularly the lungs.

In addition to the reduction in number, leukocytes not uncommonly show evidence of extensive **karyolysis.** One of the most marked karyolytic changes is that observed in the polymorphonuclear cell in pyogenic processes. The pus-cell, with its many irregularities in protoplasm and nucleus, is a polymorphonuclear cell showing the results of karyolytic change brought about by the activity of the bacterial toxins. In pronounced anemia, or in other conditions associated with blood destruction, the leukocytes may contain fragments of red blood-cells and particles of pigment derived from various sources; such cells are called *melaniferous leukocytes.* By some they are accorded great value in the diagnosis of malaria. Abnormality in color, reaction, position, size, and distribution of leukocytic granules is not uncommonly present; such variations are probably evidences of degenerative change.

Leukocytosis.—As already indicated, a wide variation in the number of leukocytes is compatible with health. Efforts to draw absolutely exact limits, beyond which the normal fluctuations do not go, have been, for the most part, illusive. If a comparatively low standard, such as 8000 or 9000, or even 10,000, to the cubic millimeter be adopted, it will be found that not uncommonly the number of leukocytes exceeds this arbitrary boundary without there being, of necessity, any evidence of disease. On the other hand, if a standard above this point, or at least very much higher, be chosen, it will be observed that in certain well-recognized morbid conditions the associated leukocytosis falls within the limit decided upon. It will thus be seen that it is quite impossible to draw a fixed line and to say that beyond this the accumulation of leukocytes is abnormal, while under this quantity the number is essentially normal. A standard of 10,000 to the cubic millimeter has been generally accepted as the maximum normal leukocytic count. There can be no objection to the figure, provided it is understood that this number is arbitrary and open to the objections just pointed out. Leukocytosis is either absolute or relative, or both. The former means an absolute increase in the number of leukocytes in the peripheral blood; the latter signifies an increase of one variety at the expense of the others.

In a general way it may be said that leukocytosis is physiologic or

VARIETIES OF

Wharton Jones. 1846.	Max Schultze. 1865.	Metchnikoff.	Ehrlich.	Kanthack and Hardy.	Hayem.	Percentage Present in Normal Blood.
Non-granular nucleated cells.	Small round cell I.	Lymphocyte.	Lymphocyte. Small	Lymphocyte.	Leukocytes of the first variety. Small type.	15 to 30.
	Large round cell II.	Macrophagocyte.	Large	Hyaline cell.	Large type.	2 to 6.
Granule cells finely granular.	Cells with finely granular protoplasm.	Microphagocyte.	Cells neutrophile in man, amphophile in some of the lower animals. [Note.—Throughout the volume I have referred to these cells as polymorphonuclear leukocytes.]	Finely granular oxyphile cells.	Leukocytes of the second variety.	60 to 72
Granule cells coarsely granular.	Cells with coarsely granular protoplasm.	Eosinophiles.	Leucocytes with α granules.	Coarsely granular oxyphile or acidophile cells.	Leukocytes of the third variety.	Rarely over two per cent.; in childhood may reach 11 to 14 per cent.
			Cells containing γ granules. "Mastzellen."	Coarsely granular basophile cells.		Rarely if ever present in normal blood, present in celomic fluids and connective tissues.
Granule cells finely granular.	Cells with finely granular protoplasm.		Basophile cells with δ granules.	Finely granular basophile cells.		Rarely exceeds .25.
			Myelocytes. Marrow cells. ("Markzellen" of German writers.)		Hypertrophied white cells.	Not present; found in bone-marrow (red) and present in blood in leukemia.

[1] After Adami's table (Allbutt's "Sys. Med.,"

LEUKOCYTES.[1]

SIZE.	FURTHER DESCRIPTION AND REMARKS.
5 to 11 μ, usually about the size of a normal red blood-cell, 7.5 μ.	Deeply staining, relatively large nucleus occupying most of the cell. Faint ring of non-granular protoplasm. Contains, rarely, basophilic granules. Both ameboid and phagocytic. The larger of these cells can not be differentiated from the hyaline cell. Lobulation or polymorphism of the nucleus rarely present.
11 to 15 μ.	Faintly staining, relatively large, round, oval, notched or reniform nucleus, slightly larger than above. Broader ring of hyaline, faintly pinkish, grayish or light blue, non-granular protoplasm. Actively ameboid and phagocytic. Nucleus sometimes surrounded by faint rim of hyaline protoplasm, outside of which basophilic granules may be present. (This reaction best brought out by eosin and methylene-blue.)
7.5 to 11 μ	This cell is also known as the polymorphonuclear leukocyte or polymorphonuclear neutrophile. It is sometimes called the polynuclear leukocyte. Irregularly staining nucleus; the nucleus is irregular, lobulated, reniform and not uncommonly like the figure 3, 5 or 7, or it may resemble the letter s, z or u. The nucleus may be apparently divided into three, five or even six parts, commonly connected by "underground" bands of chromatin; inability to demonstrate connection between the different parts of the nucleus led to the supposition that the cell was multinucleated or polynucleated. Irregularity in the contour of the nucleus is probably due to its being dried and fixed while still manifesting ameboid activity. The nucleus is rich in chromatin bands which may form a recognizable network in its interior. Protoplasm finely granular. The granules formerly believed to be neutrophile are now regarded as faintly oxyphile or acidophile. The granules are commonly demonstrable over as well as around the nucleus. The cell is actively ameboid and phagocytic. Mitotic and amitotic division of the cells is sometimes demonstrable. These cells are sometimes regarded as the adult leukocytes of the blood. They are the most important if not the only pus cell. Sometimes cells are seen in the blood partaking of the characteristics of both the mononuclear and faintly oxyphile types; such cells are sometimes spoken of as transitional leukocytes. The writer is not kindly inclined toward the use of the word "transitional." Its use is excused only by the fact that in enumerating leukocytes occasionally cells are encountered which can not be definitely placed. Reference has been made to this when considering the lymphocytes and hyaline cells, between which we believe we recognize intermediate forms. Sufficient care in staining and careful focusing will usually, although not always, enable one to differentiate between these types.
Usually smaller than the preceding type. Diameter ranges between 7 and 10 μ.	Nucleus possessing many of the characters of the preceding variety. Rarely centrally placed. Chromatin network less conspicuous, often not recognizable; cells not uncommonly clearly polynuclear without recognizable connecting or "underground" chromatin bands between the different nuclei. Horseshoe-shaped and reniform nuclei frequent. Cell protoplasm not easily identified, with the exception of the granules, which are conspicuous even in the unstained cells. Granules large, clearly defined, highly refractile, usually discrete, but may be so abundant that differentiation is not easy; they take acid stains intensely. Stain reddish-brown with Ehrlich's stain. Actively ameboid not usually believed to be phagocytic. Granules or matrix may contain bactericidal substances.
Relatively large; may exceed 20 μ.	Faintly staining, round or oval, structureless nucleus. Protoplasm usually difficult to demonstrate, may appear irregularly notched at the margin, granules slightly refractile in unstained specimens, large and abundant; stain deeply (purplish blue) with methylene-blue or with the dahlia formula.
Rarely attains size of the finely granular oxyphile cell usually much smaller.	Finely granular and coarsely granular cells are described by some writers as "mastzellen." Nucleus round or irregularly indented. Stains faintly, usually with less intensity than the granules, but of the same color. Granules like preceding variety, but very fine.
Usually 11 to 18 μ; average about 15 μ.	Pale. uniformly staining, eccentrically placed, ovoidal or round nucleus, resembling the hyaline cell. Protoplasm varies in quantity. The granules present in the protoplasm are usually not to be differentiated from the granules of the finely granular oxyphile cell. Stain reaction of the granules is not constant. Eosinophile granules and intermediate gradations of stain reaction occasionally present. Eosin and hematoxylin usually fail to demonstrate the presence of granules. Fixed by Flemming's solution, karyokinetic figures may be present. Probably identical with "cellules medullaries" of Cornil. Cabot considers them intermediate between the hyaline cell and the finely granular oxyphile cell. While found in other diseases, it is in myelogenous leukemia that the presence of myelocytes assumes great diagnostic importance.

vol. i, p. 79); modified and extended.

pathologic. The leukocytosis occurring during digestion, the leukocytosis of the new-born, which not uncommonly persists until the end of the first year, and the leukocytosis at times associated with pregnancy are taken as examples of the so-called **physiologic leukocytosis.** Digestive leukocytosis is sometimes quite marked, but ordinarily the increase is not more than 33 per cent. The cellular elements in excess are the lymphocytes and polymorphonuclear cells; sometimes the increase is more marked in one than in the other. This point is of value, as a blood examination made during digestion might, as a result of the large lymphocytic count, lead to erroneous conclusions, and the finding of an excess of polymorphonuclear cells might also mislead. When gastric digestion is deficient or greatly delayed, it occasionally happens that there is no digestive leukocytosis, and, hence, the absence of digestive leukocytosis is not uncommonly regarded as an evidence of gastric disorder. Some observers regard this leukocytosis, which is most constant after the midday meal, as largely a diurnal variation, its occurrence having been noted in fasting persons. Cabot ascribes to it no diagnostic value.

Inflammatory Leukocytosis.—This form is most frequently associated with suppurative, septic, or other inflammatory processes, and is not uncommonly preceded by a brief stage of leukopenia, the extent and duration of which depend upon the promptness with which the body tissues react, and also on the virulence of the infecting factor. The prompt occurrence of this form of leukocytosis in acute infective disorders—such as pneumonia, acute bacterial conditions affecting serous membranes, streptococcal and staphylococcal infections, scarlet fever, and allied conditions—is regarded as a favorable omen; the occurrence of a leukopenia that persists is held to be an evidence of weak resistance or of overwhelming infection. Not uncommonly the count in inflammatory leukocytosis approaches 35,000, 40,000, or 50,000, and in rare instances the number of leukocytes present may be considerably greater. The leukocyte most abundant in this condition is the polymorphonuclear cell. The large numbers of these cells present in the blood may so alter the percentage that repeated accurate observations show that from ninety to ninety-five per cent. of the leukocytes are of this type. In some cases there is an increase in the number of lymphocytes. As in other forms of leukocytosis, various opinions have been held as to the source of the added leukocytes and the essential etiology of the condition. It has been held that the leukocytosis is the result of nothing more or less than altered distribution; the polymorphonuclear cells leaving the celomic cavities and entering the blood in response to infection. While it is not improbable that such a cause may be active, the large number of leukocytes destroyed at the point of infection,—as, for example, in abscess formation,[1]—and the evidence of increased leukolysis, as shown by the excretions, point to the occurrence of increased leukocytic production.

The leukocytosis of malignant disease, syphilis, rickets, and the leukocytosis following hemorrhage, as well as that which not uncommonly precedes death (agonal leukocytosis), are by some writers grouped with the inflammatory increase of leukocytes. The leukocytosis observed in connection with malignant disease usually consists of an increase in the mononucleated forms of leukocytes; the same

[1] See p. 295.

is true of rickets, syphilis, and agonal leukocytosis, while that following hemorrhage is usually of the polymorphonuclear type. Leukocytosis is usually more marked in the presence of sarcoma than in carcinoma, and is particularly evident when the former disease attacks the lymphatic structures. The increase in leukocytes met with in cases of gout, nephritis, quinin poisoning and similar conditions, and after etherization is sometimes called **toxic leukocytosis.**

Artificially induced leukocytosis, or **leukotaxis,** has been suggested as a means of increasing local or general resistance to infection; although as yet in the trial stage, the expedient appears promising.[1] Petit augmented the resistance of the peritoneum of animals by injecting heated horse serum, and also obtained satisfactory results with human beings; Mikulicz employed subcutaneous injections of nucleinic acid before operation. The efficacy of these measures lies in the increase of polymorphonuclear leukocytes, which is said to be from 9 to 425 per cent.

Eosinophilia is a debatable term used to signify an increase of the eosinophile leukocytes of the blood. The condition is very constantly observed in many diseases of the skin, some bone affections, bronchial asthma, and myelogenous leukemia. The greatest diagnostic value of this form of leukocytosis is in connection with the presence of intestinal or other parasites, as in cases of uncinariasis, trichiniasis, hydatid disease and filariasis. Counts of eosinophiles as high as sixty per cent., or even more, of the total number of leukocytes have been recorded.

Blood-platelets are spheric, ovoid, or irregular non-nucleated bodies, from 1 μ to 4 μ in diameter, found free in the blood-plasma. Their number ranges from 180,000 to 400,000 per cubic millimeter. They disappear rapidly from blood exposed to the air, and special technic is necessary to observe them in the fresh specimen. But little is known of their origin or significance. The general opinion is that they are formed in the red cells, from nuclei or other cast-off material. They possibly originate from the nuclei of leukocytes. They are numerous in white thrombi and appear primarily active in the formation of other types of thrombus. By some they are regarded as the source of one of the elements of fibrin ferment. The platelets are increased in most of the anemias, particularly chlorosis, leukemia, pneumonia, tuberculosis, myelitis, and numerous other conditions. They are diminished in purpura, hemophilia, and many acute fevers. The platelets are well shown by Wright's stain, but are not demonstrable by Ehrlich's mixture.

Hemocytolysis or Hemolysis.—Dissolution of the red blood-cell with liberation of the hemoglobin and endoglobular changes in the cell cytoplasm not infrequently occur in a sufficiently marked form to deserve consideration as a distinct pathologic process. Blood destruction is, in a sense, normal. The liberated blood coloring-matter resulting from cell dissolution is converted, in the liver, into bile pigment, and possibly enters into other normal chemic processes. When the process exceeds the normal or when cell destruction assumes an abnormal type, the resulting condition is spoken of as **hemocytolysis, hemoglobinemia,** or by some writers as **hemolysis.** In the condition under consideration the cell elements primarily involved are the erythrocytes; when the cell destruction involves both red cells and leukocytes (erythrocytolysis and leukolysis), the term hemolysis is more appropriate.

[1] See summary of literature by Romme, "La Presse Médicale," Jan. 18, 1905.

Of the many causes presumed to be active in the production of hemocytolysis, no one satisfactorily explains the occurrence of the manifestation under all circumstances. When foreign blood is introduced into the circulation of an animal, and particularly when such blood is from an animal of another species, the added hemal cells promptly undergo fragmentation. The introduction into the circulation of large quantities of fluid may give rise to destruction of normal erythrocytes. Hemocytolysis occurs in connection with certain infectious diseases, among which may be mentioned smallpox, scarlet fever, diphtheria, enteric fever, and, possibly, to a varying extent, all the acute exanthemata. Bacteria and bacterial products circulating in the blood, as in septicemia and pyemia, may bring about the change, and a number of microorganisms have been shown to produce hemolytic poisons through the activity of which blood-destruction is accomplished. Malaria always induces more or less erythrocytolysis, and in certain forms the process assumes grave proportions. Many poisons induce a similar change, and hemolysis arising from such causes is called toxic. A long list of poisons possessing the power might be given, the most important of which would be chlorate of potash, arseniureted and phosphoreted hydrogen, carbolic acid, pyrogallic acid, and various coal-tar derivatives other than those mentioned, such as anilin, antifebrin, antipyrin, etc. The blood destruction associated with poisoning by various fungi, and, indeed, the destruction accompanying the introduction of venom, might properly be grouped with this class. Extremes of temperature seem to be influential in the production of this condition, and local tissue destruction from burns or frost-bites may bring about the change. The condition is sometimes associated with Raynaud's disease. A form of hemocytolysis is clinically recognized as **paroxysmal hemoglobinuria.**

Whatever may be the cause of the cell dissolution, liberated hemoglobin may be excreted by the kidney (**hemoglobinuria**) as methemoglobin or oxyhemoglobin, or the latter may be converted into the former by more or less prolonged retention within the bladder, and a sufficiently long stay in this organ may lead to the final conversion of oxyhemoglobin into acid hematin. An examination of the blood usually shows that it is dark in color, and the serum secured by coagulation or by the centrifuge may possess a hemoglobin tint. Blister serum obtained from the patient may show the spectroscopic lines of free hemoglobin. There is usually a marked reduction in the number of erythrocytes, associated with the presence of degenerating, fragmenting cells, chlorocytes, and achromocytes. Poikilocytosis, microcytosis, and megalocytosis are present to varying degrees. The reduction in hemoglobin may be marked. As a rule, there is little change in the number of leukocytes, although evidence of leukolysis may be present. The liver may be unequal to the task of removing the large quantity of hemoglobin, even with the occurrence of polycholia. The liver cells may manifest granular change and bile-staining; free pigment is not uncommonly present in the hepatic tissues. No constant renal lesion is demonstrable, although the kidney shows, for the most part, considerable staining, and the secreting substance may be brown or brownish-red in color; granular, desquamative, and other degenerative changes may be seen in the renal epithelium in marked cases, and free pigment may be present in the tubules; the Malpighian tufts are said to escape the

deposit. Mention has already been made of the hemoglobinuria. Hemoglobin infarcts occur in the kidneys, and infarction is occasionally present in other organs.

Regeneration of the Blood.—After extensive hemorrhage, and from other causes, direct loss and blood destruction may reduce the number of red cells to 1,000,000 or less. Usually, with the subsidence of the cause regenerative processes rapidly ensue. After the loss of blood a temporary hydremia is brought about by the abstraction of fluid from the tissues, thereby restoring the volume of the circulating medium by increasing the liquid portion. The leukocytes are rapidly replaced, probably from the tissue spaces, and often become moderately increased in number, a distinct polymorphonuclear leukocytosis occurring. Later, the mean diameter of the erythrocytes falls, and normoblasts are present in varying quantities. The fall in hemoglobin is at first proportional to the reduction in the number of red blood-cells, but later the color-index drops, and may fall as low as 0.5. During the process of erythrocytic regeneration nucleated cells may appear in varying numbers. The erythrocytes increase more rapidly than the hemoglobin, and, hence, for a time the color-index remains low.

The length of time necessary for complete regeneration of the blood varies with the recuperative and hematogenic power of the individual and with the extent of the hemorrhage. Repeated hemorrhage weakens the regenerative powers more rapidly and to a greater extent than a single copious hemorrhage. Attempts to establish a definite period within which hemal regeneration will occur are not well founded, by reason of the uncertainty in hematopoiesis in different individuals.

Anemia.—The term anemia has been variously defined, but, so far as a definition goes, nothing better has been offered than to call it "a poverty of the blood." In certain classes of cases the anemia is apparently dependent upon defects of the blood-making or blood-destroying organs, or, possibly, it would be better to say faults of hematogenesis or hemolysis, or both. Anemias in which no sufficient cause can be recognized in the organs or tissues are commonly referred to as **primary anemias.** In another class of anemias the blood condition is dependent upon some more or less evident lesion. These are the so-called **secondary anemias.** As our knowledge of pathology progresses we will, no doubt, class as secondary some of the anemias now regarded as primary. When we have demonstrated the factors influential in the production of an anemia, it becomes secondary to its demonstrated cause.

Secondary Anemia.—It is proposed to consider with this class those anemias in which it is possible to demonstrate a cause believed to be a sufficient explanation of the recognized change. As blood production is dependent largely upon the general nutrition and health of the individual, as well as upon the hematogenic functions, properly so called, it becomes evident that a large number of etiologic factors, often not even remotely associated, can be classed with the causes of symptomatic anemia. Unsanitary surroundings; improper, poor, or scanty food; overwork with insufficient food; emotional conditions influencing the appetite, sleep, etc., may all possess a varying importance in the production of anemia. Hemorrhage, copious and single, or scanty and repeated, may also be a cause. Painful affections, by reason of their

influence upon the primary and secondary assimilation, may also favor the occurrence of an anemia. Intestinal parasites—such as the Uncinaria duodenale[1] and Dibothriocephalus latus[2]—may induce anemia by interfering with the digestive process, by inducing hemorrhage, and possibly by elaborating some absorbable poison that influences unfavorably blood production or induces destruction. Anemia may depend upon the presence of parasites within the blood; the most conspicuous of these is the organism of malaria.

Acute infectious diseases commonly impoverish the blood. During the activity of such processes the anemia may not be conspicuous, but with convalescence it not uncommonly becomes evident. With this group should be classed anemias following typhoid fever, scarlet fever, smallpox, etc. So-called chronic infectious diseases are also associated with the occurrence of anemia, which may of itself be a striking symptom; the anemias of syphilis and tuberculosis are most typical. The anemia of scurvy and purpura should be mentioned. Certain of the secondary anemias are called toxic, and are dependent upon poisoning by lead, arsenic, phosphorus, mercury, etc. Malignant tumors (carcinoma and sarcoma) usually give rise to a form of anemia that may constitute an important factor in the diagnosis of such conditions.

Diseases of various organs influencing the general nutrition are not uncommonly associated with anemia. The anemias of chronic nephritis, of heart disease, and of chronic intestinal inflammations belong to this group.

The Conditions in Secondary Anemia.—The table on pages 428 and 429 gives in a general way the blood changes in this condition. It is probable that the disease ordinarily referred to as simple anemia is truly an example of secondary anemia, and that it should be considered with this group. It will be observed that the blood changes in secondary anemia possess nothing characteristic, and depend more upon the intensity of the anemia than upon any other factor. The reduction in red blood-cells varies within wide limits. A fairly evident secondary anemia may show a blood count of 4,500,000, while, at the other extreme, a count below 1,000,000 may occur. The corpuscular changes also depend upon the extent of the anemia. It may be said that in the milder anemias there is little distortion of the erythrocytes, and but few abnormal cells are present. In more marked secondary anemias poikilocytosis and microcythemia occur, while in the graver forms megalocytes and nucleated erythrocytes are found; megaloblasts are rare; normoblasts are more abundant. Polychromatophilia (abnormal stain reaction) is usually proportionate to the degree of the anemia.

The hemoglobin always shows greater reduction than the erythrocytes (low color-index), and may not exceed twenty per cent. The leukocytes are but little, if at all, influenced by the mere occurrence of secondary anemia. The condition that produced the anemia may determine a leukocytosis the character of which will depend upon the cause. It is usually stated that when the blood counts are low, a leukocytosis is likely to be present; this is not, however, an invariable rule.

The visceral lesions associated with this form are dependent upon the cause and upon the extent of malnutrition. Granular changes occur in glandular viscera, notably the kidney and liver. A similar

[1] See p. 205. [2] See p. 201.

change is seen in the heart; sometimes the myocardium will be found distinctly fatty. Degenerative changes in the capillary system are indicated by the concomitant edema. The degenerative lesions are probably dependent upon overwork of the organs involved, associated with poor nutrition, and possibly to a greater extent upon the toxic effects of poisons generated within the blood or arising from other causes and acting themselves as causes of the existing anemia.

CHLOROSIS.

Synonyms.—Febris Amatoria; Greensickness; Morbus Virgineus; Chloremia; Chloranemia; Bleichsucht (German).

Chlorosis is almost exclusively a disease of young women, marked by moderate reduction in the number of erythrocytes and greater diminution of the hemoglobin.

Causes.—As just stated, the disease is practically restricted to women, and is most frequent between the ages of fourteen and eighteen years, although it occasionally appears later in life (*chlorosis tarda*). A condition closely resembling chlorosis is sometimes seen in men. A family tendency to tuberculosis, faulty hematogenic power, or heredity, as indicated by cases appearing in successive generations, may be predisposing factors. Emotions, such as grief, fear, anxiety, homesickness, and disappointed love, have been regarded as causes. Hypoplasia of the heart and greater vessels, and sometimes of the generative organs, has been observed. Autointoxication, constipation, menstrual disturbances, unsanitary surroundings, overwork, and faulty or insufficient diet may cause or predispose toward the condition. Hemorrhage, as by epistaxis, menorrhagia, and bleeding from hemorrhoids, the intestines, or stomach, are often assigned as etiologic factors. Race and climate, particularly among civilized nations, seem to have no influence upon the occurrence of this malady. Lloyd Jones believes that the disease is more common in girls belonging to large families, and that it not uncommonly constitutes part of a general condition one of whose manifestations is unusual fertility. Grawitz regards the disease as a neurosis; von Noorden and Immermann would limit the term chlorosis to a congenital or aquired functional weakness of the hematopoietic structures dependent upon the lack of an internal secretion of the sexual organs. Dyspepsia and constipation associated with the disease are generally not regarded as etiologic factors, although one of the toxic theories (autointoxication) is based upon the belief that the blood condition is due to copremia or some allied state. In the present state of our knowledge theories suggesting an infectious origin are not regarded with favor.

Blood Changes.—The blood is easily obtained, flows freely, and is usually pale in color. The specific gravity of the serum is normal or higher than normal, while the diminished hemoglobin gives an unusually low (1040) total specific gravity. Alkalinity may be slightly increased. Coagulation is rapid. There is an oligocythemia that varies within wide limits, and is not commonly marked, oligochromemia being the most evident change. In mild cases the erythrocytes fall to eighty per cent. of the normal and the hemoglobin to fifty per cent.; in more marked instances the erythrocytes approach fifty per cent. of the normal and the hemoglobin thirty per cent. or less. The averages of the

357 cases of Cabot[1] and Da Costa[2] are: erythrocytes, 3,934,000; hemoglobin, 43.6 per cent. Hayem has reported a case in which the red blood-cells fell to twenty per cent. and the hemoglobin to sixteen per cent. It will thus be seen that the reduction in hemoglobin is always greater than the corpuscular reduction (low color-index). In about forty per cent. of the cases the number of red blood-cells does not fall below 4,000,000. The erythrocytes show a mean reduction in diameter, and are strikingly pale. Microcythemia, poikilocytosis, and polychromatophilia are present to a varying extent. Nucleated red cells are rarely abundant, although occasionally a few normoblasts occur. The presence of macroblasts is usually regarded as an unfavorable sign. The platelets are considerably increased. There may be no important change in the leukocytes, with the exception of the occasional occurrence of myelocytes in grave cases. Relative lymphocytosis may occur. (See table, pp. 428 and 429.)

Associated Lesions.—The panniculus adiposus is usually abundant and the general nutrition, aside from the pallor, seems fair or even good. The pallor of all the tissues may be striking. Granular and fatty changes occur in the heart, and aortitis is occasionally present. Hypoplasia of the heart and aorta has already been mentioned. Fatty changes in the capillary, renal, and gastric cells have been noted. Venous and capillary thrombosis and thrombosis within the cranial sinuses not infrequently occur. The morbid anatomy and blood changes fail to explain the peculiar venous hum observed during life. Changes in venous caliber, and in the blood itself, as causes of this important phenomenon deserve mention, although the demonstration is by no means satisfactory.

PERNICIOUS ANEMIA.

Synonyms.—Addison's Causeless Anemia; Idiopathic Anemia; Essential Anemia; Progressive Pernicious Anemia; Myelogenic Anemia; Ganglionic Anemia; Anœmatosis; Biermer's Disease.

Pernicious anemia is a morbid condition associated with excessive hemolysis and inadequate hematogenesis (West), and for which no sufficient cause has been demonstrated. While an adequate cause has not been recognized, certain predisposing elements are regarded as important factors in the production of disease; of these predisposing causes the following may be mentioned: pregnancy, parturition, starvation, hemorrhage, degeneration of the mucous membranes of the alimentary canal, and intestinal parasites, especially the Dibothriocephalus latus. The disease is more frequent in adults, although cases in children have been reported. Dana[3] reports a case which he believes justifies the conclusion that congenital weakness of the blood-making organs may predispose to the occurrence of pernicious anemia.

Blood Changes.—The blood is often difficult to obtain, pale, and watery, although occasionally it assumes a coffee or chocolate color. A drop forming at the point of puncture is usually not rounded and elevated, as normal, but flattened, and may spread over the adjacent

[1] "Clinical Examination of the Blood," 5th ed., 1904.
[2] "Clinical Hematology," 2d ed., 1905.
[3] "Med. Rec.," Dec. 1, 1900.

surface. Oligocythemia is marked; blood counts below 1,000,000 are not infrequent, while a count as low as 143,000 has been reported by Quincke. Occasionally, blood counts may, for a time, approach the normal, rising to or exceeding 5,000,000, followed by relapse and death. Though microcytes are present, the average size of the erythrocyte is increased, and may reach 10 μ, or even 11 μ. Megalocytes possessing diameters between 10 μ and 16 μ occur. The percentage of these large cells in severe cases may range from forty to seventy, and Ewing[1] studied a case in which at least ninety per cent. of the cells measured from 11 μ to 16 μ. He states that unless at least thirty-three per cent. of the red cells are distinctly oversized, the diagnosis of pernicious anemia should be made with reserve. Nucleated red cells are present at some time during the course of essentially every case of pernicious anemia; in the great majority of cases megaloblasts predominate over the smaller forms. Even the megaloblasts are usually present in very small numbers, and a prolonged search should be made before their absence is deemed conclusive. They not uncommonly appear in larger numbers shortly before death, and for this reason an increase is generally regarded as an unfavorable sign. So-called crises occur in which an unusually large number of normoblasts may be thrown into the circulation, followed by an increase in the number of red cells. Free nuclei are sometimes present in the blood, and occasionally one sees a nucleus with shredded protoplasm containing hemoglobin, attached to its periphery. Both normal and abnormal sized red cells may show polychromatic reactions or granular basophilia. By reason of the irregularities in the size and contour of the erythrocytes, rouleaux formation is peculiar. Oligochromemia does not approach in extent the oligocythemia. The relatively high color-index—not infrequently above the normal—is usually held to depend upon the large number of red cells the diameter of which exceeds that of the normal erythrocyte; and as the more marked the anemia, the more abundant such cells become, it is commonly found that the fall in corpuscles is not associated with a corresponding fall in hemoglobin, and that the corpuscular count may be ten per cent. of the normal or less, and the hemoglobin from fifteen to twenty per cent. of the normal or more. The specific gravity of the total blood is decreased; the platelets are sometimes increased, and occasionally show peculiar and excessive agglutination. The leukocytes are usually decreased and pronounced leukopenia is not uncommon; accompanying this in the majority of cases is a relative lymphocytosis. Myelocytes are almost constantly present, but in small numbers, rarely exceeding two or three per cent. of all the leukocytes. Leukolysis and tinting of the protoplasm of the white cells by hemoglobin may be recognized in some cases. So far as the blood-picture is concerned the present conception of the disease is that it is a megaloblastic anemia. The term "aplastic anemia" has been applied to cases clinically resembling pernicious anemia but in which regenerative changes in the bone-marrow are inadequate or absent. (See table, pp. 428 and 429.)

Associated Lesions.—In spite of the extreme anemia, emaciation is not present. The skin is pale, but may show a faint icterus; a peculiar lemon hue may be manifest in the conjunctiva. Petechiæ are occasion-

[1] "Clinical Pathology of the Blood," 2d ed., 1903.

ally present. There is not uncommonly a small amount of edema, particularly in the lower extremities. The panniculus adiposus may be abundant; it is usually yellowish in color, contrasting strongly with the red muscles. Coagulation of the blood in the great vessels and in the heart may be delayed or absent. The presence of free hemoglobin in the blood-serum and in the serous fluids is often marked and may be sufficient to stain the hands. Fatty and granular changes occur in the heart.[1] Similar degenerative processes are occasionally seen in the arteries and capillary walls. Atrophy of the gastric mucosa has been described. The spleen and kidneys may show pigmentation. Degenerative changes occur in the spinal cord, particularly in the posterior columns and to a less degree in the lateral tracts; the sclerosis is not systemic, although it may appear so. The bone-marrow usually shows reversion to the fetal state, and contains a large number of nucleated hemoglobin-containing cells (erythroblasts); the larger cells may show evidence of phagocytic power. The liver is usually enlarged and may be fatty, and constantly contains an excess of iron derived from disintegrated erythrocytes. Normally, the percentage of iron in the liver is from 0.078 to 0.12, while in pernicious anemia it not uncommonly reaches 0.7. The iron is distributed in the hepatic cells at the periphery of the lobule, where it is usually abundant. Occasionally, an excess of iron will be found deeper in the lobule, and at times the interlobular tissue may contain a trace.[2]

It is generally conceded that, though specific hemolysins have not been demonstrated, pernicious anemia, essentially, is due to an excessive hemolysis. This is indicated by the occurrence of disintegrated cells, microcytosis, polychromatophilia, plasmorrhexis, etc.; the hepatic changes offer additional support to this theory, and also indicate that the hemolysis occurs within the portal circulation. The large percentage of iron in the liver supports this view, and the absence of hemoglobinuria would indicate that the hemocytolysis did not occur in the general circulation.

LEUKEMIA.

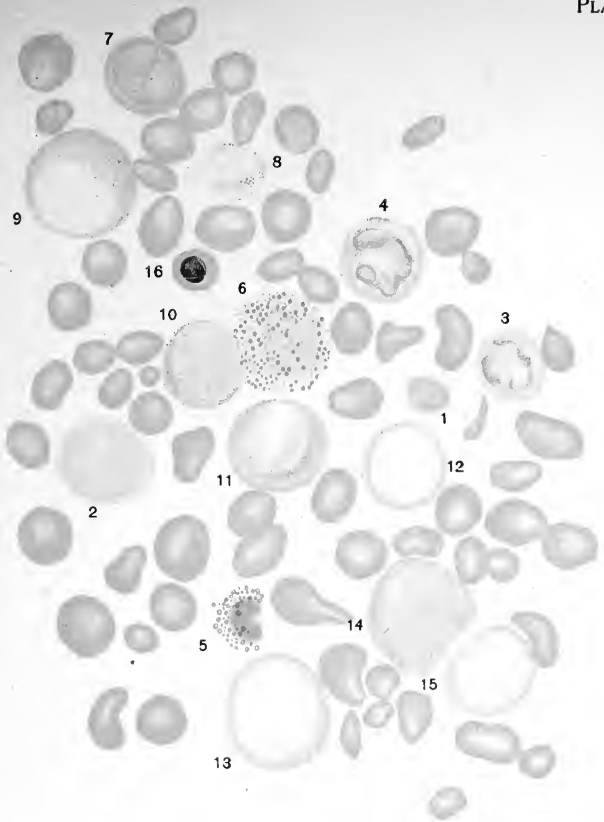
Synonyms.—Leukocythemia; Lymphadenia.

In this disease there occurs a most marked increase in leukocytes, which, while it varies within wide limits, is usually a constant feature throughout the disease. Leukemia is occasionally observed in the lower animals, notably the cat, dog, ox, sheep, and hog.

Causes.—Leukemia may occur at any age. It is most frequent during middle life—thirty to fifty years. It is twice as frequent in man as in woman. A history of malaria is present in a certain percentage of cases. Injury to the spleen is sometimes followed by leukemia. Pregnancy, lactation, rickets, and syphilis sometimes antedate the appearance of symptoms. The scanty evidence regarding heredity does not favor the view that it is an important factor. Certain facts in the history of some cases would indicate the possibility of its being an infectious disorder, but though protozoa and various bacteria have been described as present in the blood, and though it is claimed that the disease

[1] See Fig. 142, p. 244.
[2] For demonstration of iron in tissues see p. 236.

PLATE VII.



SPLENO-MEDULLARY LEUKEMIA.

(*Triacid Stain.*)

(From Da Costa's "Clinical Hematology.")

1. **Small Lymphocyte.**
2. **Large Lymphocyte.**
   Contrast this cell with the myelocytes, 10, 11, and 12, noting the presence of neutrophile granules in the latter, and their absence in the lymphocyte. The size and nuclear characteristics of all these cells are practically the same.

3, 4. **Polynuclear Neutrophiles.**

5. **Eosinophile.**
   In this "dwarf" eosinophile, ruptured during the preparation of the specimen, the granules are peculiarly arranged about the nucleus; no signs of protoplasm are distinguishable.
6. **Eosinophilic Myelocyte.**
   Note the irregularity with which the granules are stained.

7, 8, 9, 10, 11, 12, 13, 14, 15. **Myelocytes.** (*Neutrophilic.*)
   These cells vary greatly in size (compare 8 with 9), but they all have similar distinctive characteristics—a large opalescent nucleus containing a scanty chromatin network embedded in a cell body crowded with delicate neutrophile granules, precisely like those found in the polynuclear neutrophiles, 3 and 4. The nucleus of 7 is distinctly indented and somewhat denser than that of the other myelocytes. This cell probably represents a developmental phase of the myelocyte just short of its transition into a typical polynuclear neutrophile.

16. **Normoblast.**
   The erythrocytes (stained orange) show many evidences of deformity, an occasional megalocyte, many microcytes, and a few poikilocytes being present. Polychromatophilia is absent.

(E. F. FABER, *fec.*)

has been communicated to lower animals, the evidence must be regarded —for the present, at least—as incomplete; experienced investigators have failed to demonstrate bacteria in the blood, and by them inoculation in animals has proved futile. By some the process, especially in the acute cases, is regarded as allied to tumor formation. This view would regard the blood as a tissue the intercellular substance of which is fluid, and the added cellular elements present in the blood would be considered tumor cells. The fact that the cells invade the organs, or at least are found infiltrating various organs and tissues, is adduced to support the theory. Nothing satisfactory in the way of demonstration has been given, and at best the view can be looked upon as a working hypothesis only.

Two forms of the disease are recognized—(1) myelogenous and (2) lymphatic. Clinically, either may be acute or chronic. The myelogenous is almost always chronic; the lymphatic is not infrequently acute.

The Blood Condition.—When the number of leukocytes is large, the blood may be pale, and even slightly turbid, and marked oligocythemia, with associated reduction in blood coloring-matter, may give rise to a thin, watery consistence, and, as a result of the presence of a large number of leukocytes, a yellowish tint. The platelets are increased, the alkalinity lowered. Coagulation is delayed, and this delay is most notable in the presence of pronounced oligocythemia and oligochromemia. The actual quantity of fibrin present is said to be increased. The two statements are reconciled by the belief that peptone is present, which, as is well known, delays coagulation.

Myelogenous Leukemia (*Myeloid Leukemia or Leukocythemia; Myelemia; Myelocythemia*).—The total number of leukocytes shows a wide variation, the majority of cases being included between 100,000 and 500,000; counts between the latter number and 1,000,000 are not infrequent, and as high as 1,590,000 has been recorded. The average in the 108 cases of Cabot and DaCosta was 370,000. The enormous addition of myelocytes is the most conspicuous change in this form of the disease. These cells may constitute from twenty to fifty per cent. of the leukocytes present—a percentage never approached in any other form of leukocytosis. They vary remarkably in size, from 7 μ to 20 μ or more in diameter. Owing to the frequency of degenerative changes in the leukocytes in this disease, the differentiation of myelocytes and lymphocytes is in many instances very difficult. Mast cells with coarse granules are almost constantly conspicuous, ranging from one to ten per cent., or even higher. Next to the myelocytes they are probably the most important diagnostic feature. There is a marked absolute increase in the eosinophiles and polymorphonuclear leukocytes, although the preponderance of myelocytes materially alters the percentage. Instead of from sixty to seventy per cent. of the leukocytes belonging to the polymorphonuclear group, the percentage varies between ten and fifty. The uninuclear cells, lymphoid and hyaline, are relatively diminished Myelocytes showing karyokinesis are occasionally present.

The red cells are usually diminished in number; the extent, however, of the reduction varies in different cases, and more or less at different periods in the history of any given case. Sometimes the count may be normal; in other cases the oligocythemia may be most marked.

Eichhorst has reported a case in which the red cells were reduced to 316,000 to the cubic millimeter. The reduction in red cells proportionately reduces the hemoglobin; marked alterations in the color-index are not uncommonly present. A conspicuous morphologic change is the abundance of nucleated red cells. Normoblasts are rarely absent; microblasts and megaloblasts are never so abundant. Poikilocytosis is not commonly conspicuous. The blood-platelets are commonly increased. Charcot-Leyden crystals are occasionally seen. (See table, pp. 428 and 429.)

Lymphatic Leukemia (*Lymphocythemia; Lymphemia*).—Leukocytosis is not so marked as in myelogenous leukemia. The total count of leukocytes ranges between 40,000 and 400,000, rarely exceeding 200,000 or 250,000, although counts of more than 1,000,000 have been reported. The average in the thirty-five cases of Cabot and Da Costa was 255,000. The leukocytes most abundant in this form are the uninuclear cells; in some cases the lymphocyte, in others the hyaline cell, predominates. The polymorphonuclear cells are diminished; the eosinophiles are scanty or absent. Myelocytes, if present, are never abundant. Oligocythemia is more conspicuous and constant in this form of leukemia. The count of the red cells may show from 1,000,000 to 2,000,000. Abnormal forms of red cells correspond to the degree of anemia. Nucleated erythrocytes are not so numerous as in the myelogenous form of the disease. (See table, pp. 428 and 429.)

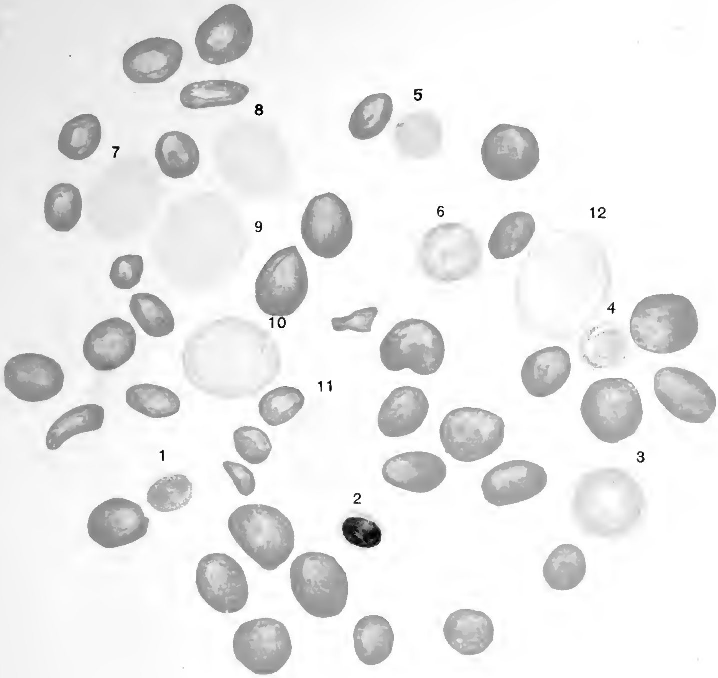
In the chronic, and usual, variety of this form of leukemia the small lymphocyte commonly predominates, although the large lymphocyte may be in excess. The average is about ninety per cent. of the entire number of leukocytes. Atypic forms of lymphocytes are often numerous.

The acute variety terminates fatally within a few weeks or months after its onset, and in many ways resembles an acute infection; a specific cause, however, has not yet been demonstrated. In the greater number of cases the large lymphocyte predominates, an excessive leukocytosis not always being present. Conspicuous accompanying lesions are cutaneous, mucous, and visceral hemorrhages, and ulcerative stomatitis.

The names given to the different forms of leukemia are not based upon changes in the organs; enlargement of the lymph-nodes is not a constant feature of lymphatic leukemia and marked changes in the bone-marrow may be present. Changes in the organs usually depend upon the duration of the disease rather than upon the character of the blood-cells, being more marked in chronic cases.

The spleen may be greatly enlarged, weighing as much as eight kilos. The capsule may be fibrous or even cartilaginous. The shape of the organ is not altered. Infarcts may be recognized upon the surface or on section. Associated infectious processes produce less softening in the leukemic organ than in the normal spleen. The color of the pulp is further influenced by the number of red blood-cells, and as leukemic patients are prone to hemorrhage, a pinkish or pale pulp may be induced thereby. In the absence of such condition the pulp is usually redder than normal. The extensive intercalation of leukocytes may, even in the paler pulp, obscure the Malpighian bodies. As already stated, the density of the organ is more marked in the chronic form of the disease. Under the microscope the splenic reticulum may be somewhat increased, although it is not commonly much in excess of

PLATE VIII.



LYMPHATIC LEUKEMIA.

(*Triacid Stain.*)

(From Da Costa's "Clinical Hematology.")

1, 2, 3, 4, 5, 6. **Small Lymphocytes.**
These cells show a great difference in the intensity of their reaction toward the basic dye. The smallest forms, 1, 2, 4, and 5, being richer in nuclear chromatin and staining more deeply than the larger, 3 and 6. Compare 2 with the normoblast, 16, Plate V.

7, 8, 9, 10, 11. **Large Lymphocytes.**
Except in 10, which shows a delicate rim of fuchsin-stained protoplasm, these lymphocytes appear simply as pale chromatin-deficient nuclear structures, lacking cell bodies. Compare these cells with the myelocytes, Plate V.

12. **Transitional Form.**
The upper edge of the nucleus is somewhat indented and the protoplasm is di tinguishable; otherwise this cell resembles a large lymphocyte.

(E. F. FABER, *fec.*)

the normal. Occasionally, it shows more or less hyaline change. The most striking feature is the abundance of leukocytes. These are usually of the form in excess in the blood. The more chronic the case and the greater the splenic enlargement, the more marked the leukocytic intercalation.

The changes seen in the bone-marrow usually assume one of two types, although intermediate grades are occasionally noted. Both of these types have received inappropriate names. *Pyoid marrow* is yellowish in color and soft in consistence. The marrow usually present is firm, pink or pinkish-gray in color, and is called *adenoid* or *lymphoid marrow*. The abnormal marrow displaces the fatty medulla of the long bones. Histologic changes of the myelogenous form consist of an enormous increase in the number of normal marrow-cells. Erythroblasts, normal in size, and cells of the larger and smaller types, are usually found; large phagocytic marrow-cells are present. Evident cell proliferation is not uncommonly present, and in a few cases has been conspicuous. The gross appearance of the marrow in lymphatic leukemia does not differ from that observed in the myelogenous cases. The leukocytes present are, however, of the hyaline and lymphocytic types—normal marrow-cells being displaced by the lymphoid infiltration.

Lymph-nodes.—In nearly all cases of lymphatic leukemia enlargement of these structures occurs at some time or other in the progress of the disease. In some cases the enlargement is restricted to an anatomic group; in other cases different areas may be involved; and still less frequently the condition may be general. On section, the affected nodes are pink or grayish-pink in color, soft, and juicy. Confluence is not common, and even where a large group has apparently merged into a single mass, differentiation of the nodes may be possible. The enlargement of the nodes seems to be due to engorgement of the lymph-channels, including the peripheral sinuses. In the less frequent glandular enlargement of the splenomedullary form the lymphatic sinuses are distended by leukocytes presumably coming from the blood.

The liver usually shows considerable enlargement, and may weigh as much as eight kilos. It is commonly pale, and the pallor may be most conspicuous along the course of the portal channels. The extreme anemic appearance is frequently due to the intercalation of leukocytes, the distribution of which may be patchy, local, or general.

The kidneys may be enlarged. and lymphoid intercalation may be marked.

Increase in the lymphoid tissue is always noticed in the thymus and the lymphoid elements of the alimentary canal, as well as in the lungs, and even in the skin. The tendency toward hemorrhage, previously remarked upon as a clinical phenomenon of leukemia in general, is further shown by the occurrence of visceral hemorrhage and of hemorrhage into the newly formed areas of lymphoid tissue, into the joints, and even into the brain.

No satisfactory explanation has been offered for the increase in leukocytes and the associated intercalation of these cells in the various organs. It has been held that the leukocytic increase is dependent upon proliferation of the lymphoid tissue from which leukocytes are thrown into the general circulation. It has also been maintained that the lymphocytic infiltration of the various organs and tissues represents

DISEASES.			Gross Appearance and Sp. Gr.	Hemoglobin and Color Index.	Number of Erythrocytes.	Size of, and Form Changes. in Red Cells.
Primary Anemias.		Chlorosis.	Blood flows readily. Pale red, watery. Extravascular coagulation slow; intravascular, frequent. Sp. gr. of total blood decreased. Sp. gr. of plasma slightly increased.	Hemoglobin greatly reduced. Color index constantly low.	Normal or slightly reduced.	Decreased in size. Poikilocytosis only in severe cases and rarely marked.
Primary Anemias.		Pernicious Anemia.	Blood flows scantily, often difficult to obtain. Watery, pale red (often coffee color). Coagulation slow. Sp. gr. decreased.	Marked reduction in the amount of hemoglobin. Color index usually high.	Pronounced oligocythemia. Rouleaux formation scanty or absent.	Marked variation in size. Macrocytes predominate. Poikilocytosis more marked than in any other anemia.
Primary Anemias.		Simple Primary Anemia.	Paler red than normal. Coagulation slightly more rapid. Sp. gr. decreased.	Hemoglobin moderately reduced. Color index normal or nearly so.	Moderately diminished.	Normal or slightly decreased in size.
Primary Anemias.	Leukemia.	Myelogenous Leukemia.	Light red or milky. Less fluid, coagulation slow. Sp. gr. decreased. Alkalinity usually diminished.	Hemoglobin slightly reduced. Color index below normal.	Usually only a slight reduction.	A slight reduction; poikilocytosis slight.
Primary Anemias.	Leukemia.	Lymphatic Leukemia.	Resembles myelogenous type, except that changes are not so pronounced. Alkalinity usually diminished.	Hemoglobin reduction more marked than in splenomedullary type. Color index low.	Reduced. Always more pronounced than in myelogenous type.	Reduction in size, and distortion more striking than in myelogenous type.
Primary Anemias.		Pseudo-leukemia or Hodgkin's Disease.	Paler red than normal, depending on severity. Coagulation more rapid. Sp. gr. normal or slightly decreased.	Hemoglobin reduced, depending on severity and stage. Color index normal or low.	Diminished, depending on severity and stage.	May be undersized. Poikilocytosis in severe cases.
Primary Anemias.		Splenic[1] Anemia.	Pale red, more watery. Coagulation more rapid. Sp. gr. decreased.	Hemoglobin reduced. Color index normal or low.	Reduced sometimes to one-fourth of normal.	Normal; usually slightly reduced. Poikilocytosis seldom excessive.
Secondary Anemias.			Pale red, depending on severity; watery. Coagulation usually rapid. Sp. gr. decreased.	Reduction varies, depending on severity. Color index usually below normal.	Diminution varies with condition.	Usually decreased. Poikilocytosis in a number of severe conditions.

[1] By some authors not recognized as a primary anemia.

CHANGES IN ANEMIAS.

Nucleated Red Cells.	Number of Leukocytes.	Large and Small Lymphocytes.	Polymorphonuclear Leukocytes.	Myelocytes.	Blood-platelets.
Rarely found. Normoblasts are present in severe cases.	Generally normal.	Occasionally relatively increased.	Normal or relatively diminished.	Rarely found.	Increased.
Microblasts, normoblasts, and megaloblasts present. The latter most numerous.	A moderate leukopenia may be present.	Usually relatively increased.	Commonly decreased, relatively.	Small number nearly always found.	Diminished.
Only in severe cases.	Generally normal.	Sometimes increased relatively.	Sometimes decreased relatively.	Absent or rare.	Increased.
More frequent than in any other form of anemia. Normoblasts predominate.	Enormous increase. In no other anemia are leukocytes so abundant.	Increased, but relatively diminished.	Increased, but relatively diminished.	Myelocytes form a large percentage of the leukocytes, from 10 to 60 per cent. or more. (Basophilic cells included.)	Increased.
Rarely present.	Greatly increased, but not to the extent found in the myelogenous type.	Greatly increased (as high as 90 per cent. or more). Sometimes small and other times large are increased.	Relatively decreased.	Absent or rare.	Increased.
Usually absent. May be present when disease is marked.	Normal or slightly increased.	Generally normal.	Generally normal.	Rarely found.	Increased.
Rarely present.	Normal or slightly increased.	Generally normal. Usually increased if fever is present.	Generally normal.	Rarely found.	Increased.
Rarely met with in mild anemias, but not uncommon in pronounced cases.	Generally increased. Seldom normal or decreased.	Usually diminished.	Usually increased.	May be found in some cases.	Usually increased.

the accumulation of leukocytes deposited from the blood. White and Hopkins favor the belief that the increase in leukocytes results from diminished destruction of the cells.

Pseudoleukemia (*Hodgkin's Disease*).—This morbid condition resembles leukemia in its anatomy, but differs materially in the blood changes. The latter are not characteristic, the chief value of the blood examination lying in the absolute exclusion of leukemia. In the early stages the blood shows no noteworthy departure from the normal; later a variable degree of anemia ensues. The leukocytes remain unchanged or moderately increased; there may be a relative gain in polymorphonuclear leukocytes or in the lymphocytes. Like leukemia, the disease may assume an acute form, but usually is chronic in type. Splenic enlargement may predominate over the changes in the lymph-nodes.[1]

Splenic anemia—sometimes called *pseudoleukemia splenica*—is regarded by some as a splenic form of Hodgkin's disease analogous to the myelogenous form of leukemia. The anemia is of the chlorotic type. Leukopenia, sometimes pronounced, is the most characteristic finding. Relative lymphocytosis is common. The changes in the blood in pseudoleukemia and in splenic anemia, and their differentiation from leukocythemia, will be found in the table on pages 428 and 429.

Mycoses of the Blood (see Intoxications and Infections, pp. 376 and 377).—The possible infections of the blood may be greater than is at present believed. The organisms of anthrax, tuberculosis, glanders, typhoid fever, and relapsing fever, also the pyogenic and a few other bacteria, have been identified in the blood. Care must be used in drawing conclusions from the presence of bacteria in the blood postmortem, as it has been satisfactorily demonstrated that in the agonal period—the final moments or, it may be, hours of the death agony—bacterial diffusion is favored by the lessening bactericidal action of the blood and the probable increasing permeability of the vessel walls. The demonstration of bacteria in the blood does not materially differ from their demonstration elsewhere. Trustworthy conclusions are rarely possible from an examination of a drop of blood obtained by simply pricking the skin, as already directed. The method of Sittmann is to be commended. A vein, preferably one in the arm, is exposed under the most rigid aseptic methods,—previous sterilization of the skin, instruments, operator's hands, etc.,—and a sterile cannula is thrust into the vessel, which may be caused to distend by proximal obstruction, as by pressure by the finger or a fillet applied above the point elected for opening. The blood flowing from the cannula is received in a sterile container (flask or test-tube sterilized by heat), and the subsequent examination is conducted upon principles laid down in the chapter on Bacteriologic Technic.

Animal Parasites.—The animal parasites found in the blood are broadly classed as hematozoa. The most important are the malarial organism (p. 186), the embryo of the Filaria sanguinis hominis (p. 207), the trypanosoma (p. 183), the spirochæta of relapsing fever (p. 172), and the Distoma hæmatoba (p. 193). The last named is really a parasite of certain vessels—the portal vein and its branches and the venous ramifications around the bladder and rectum.

[1] For further consideration of the morbid anatomy of Hodgkin's disease see Diseases of the Lymph-nodes.

CHAPTER II

SPLEEN.[1]

The **spleen,** in the course of the postmortem, is the first organ examined in the abdominal cavity. It varies greatly in size and weight, usually weighing between 100 gm. and 350 gm., and measuring from 10 cm. to 15 cm. in length, 6 cm. to 10 cm. in breadth, and 2.5 cm. to 4 cm. in thickness; the relation to the weight of the body is about 1 to 360. The color varies considerably, even in health, and undergoes important changes after death; the same may be said of the consistency.

Postmortem Changes in the Spleen.—In the presence of any engorgement or necrotic process the spleen quickly undergoes postmortem disintegration. As a result of attachment to the stomach, digestion may give rise to disintegration of the gastric wall which sometimes extends into the splenic tissue. Sulphureted hydrogen passing through the wall of any adjacent hollow viscus gives rise to precipitation of the iron present in the splenic tissue, as a result of which the organ shows *pseudomelanosis*, at first restricted to the area of contact, but in time, and particularly where decomposition is in progress, involving the whole surface of the organ. The layer of postmortem pigmentation is usually thin, rarely extending to a depth of one centimeter.

Emphysema of the spleen, with or without the presence of gas cysts, is a postmortem process, and depends upon the evolution of gas in the splenic pulp as a result of infection by some gas-producing organism, such as the Bacillus aerogenes capsulatus, colon bacillus, etc.

Malposition.—Splenoptosis, *wandering* or *movable spleen*, arises as a result of relaxation or stretching of its normal attachments, and usually the organ is one of several displaced in the condition called **splanchnoptosis,**[2] *visceroptosis*, *enteroptosis*, or *Glénard's disease.* Visceral prolapse, of which splenoptosis is a type, may result from developmental defects, external compression, as by improper corsets and belts, or may occur in patients who have been bed-ridden, in whom it is a result of muscular wasting and relaxation. The postpartum cases are due to overdistention of the abdominal wall by a number of pregnancies. Postoperative forms result from similar relaxation of the belly wall. The spleen may also be displaced by blows or injuries which suddenly force the costal margin inward. It is not improbable that falls in the erect posture or on the buttocks may jar the spleen from position. The extent of the splenic displacement may be very marked, the viscus at times becoming a pelvic organ. It is probable that the lengthening of the suspensory ligament may be caused by an increase in the size of the spleen, and,

[1] Lectures on Disorders of the Spleen, Taylor, "Lancet," May 28, 1904, p. 1477.

[2] Robinson, "Phila. Med. Jour.," Nov. 30, 1901. Keith, "Lancet," March 7, 1903, p. 631. Brown, "Amer. Med.," Aug. 15, 1903, Aug. 22, 1903, p. 307, and Aug. 29, 1903, p. 359. McCallum, "Brit. Med. Jour.," Feb. 18, 1905, p. 345. Gallant, "International Clinics," 1905, vol. iv, 14th series.

most certainly, the displaced organ becomes larger, the increase in size being partly due to the obstruction to venous return, brought about by the tension on the splenic vein impeding the flow of blood on its way to the liver.

The condition is more common in the female than in the male, and is most frequent in women who have borne a number of children. Relaxation of the abdominal wall favors displacement of the organ by partial withdrawal of its normal support. The spleen may be forced from its normal position by spinal curvature, tumors and swelling in the retrosplenic area, and assumes a lower level as a result of inflammatory effusion, morbid growths, etc., in the left pleura. The organ is sometimes pulled out of place by attachment to an adjacent prolapsed viscus, as the colon, stomach, kidney, or pancreas. The long pedicle necessary for such marked displacement as is seen when the spleen is located in the pelvis or in the right iliac fossa is usually made up of the splenic artery and vein, with a certain amount of connective tissue, in which may be embedded a part of the pancreas. The danger in wandering spleen is twisting of the pedicle and obstruction to the blood-supply of the displaced organ. Interference with the venous circulation may be brought about slowly inducing congestion, with marked induration of the spleen (*cyanotic induration*). It is alleged that the interference with circulation may give rise to atrophy, although I have never seen the two conditions associated. When the obstruction, either venous or arterial, is complete, necrosis, which may be manifested as a general softening of the organ or as gangrene, occurs. The liability of wandering spleen to circulatory disturbance is further evinced by the fact that it not uncommonly contains infarcts; these may be of different ages. As a result of localized peritoneal inflammation and capsulitis, the wandering spleen may become attached in some abnormal position, and has been mistaken for a neoplasm arising at the point of attachment.

In addition to the wandering spleen, there is occasionally seen, as in the liver, a partial rotation of the organ on its long axis, thus presenting an edge for percussion and other physical examination, and misleading the clinician as to the size of the organ. In the *situs inversus* the organ is absent, prolapsed, or on the right side.

Malformation.—The spleen may be absent. *Hypoplasia* of the organ is more common. *Splenculi*, or *accessory spleens*, are quite frequent. The number of splenculi varies. Usually one or two are found. Instances have been reported, however, in which as many as forty accessory spleens were present. It is probable that, in the cases where hundreds of splenculi[1] have been reported, hemolymph nodes, normal or enlarged, have been mistaken for spleens. The accessory organs may be situated near the hilum of the normal organ, in the splenic pedicle, in some peritoneal fold adjacent to the spleen, or even upon the opposite side of the abdominal cavity. Rarely, they are found in the spleen itself, and are occasionally embedded in other organs, as the pancreas. Histologically, the structure of the accessory organs is identical with that of the normal viscus, the former being nothing more than miniature reproductions of the latter. They are probably physiologically accessory to the normal spleen, and may undergo hypertrophy after removal of the fully formed organ. It has usually been found that where animals

[1] "Münch. med. Woch.," 1895, No. 18. p. 433.

show no disturbance of health as a result of splenectomy, accessory spleens have hypertrophied and have assumed the function of the removed organ.

Instead of a single organ approaching the normal, with a number of accessory spleens, there are sometimes found two or more smaller organs of approximately the same size, **multiple spleens.** Garrod has observed nine spleens in one cadaver. Multiple and accessory spleens are liable to the same diseases as the normal organ.

The normal splenic notch may in rare instances be absent, and in other cases a number of notches are found. Occasionally, the normal notches are deep, and practically amount to incisures or fissures, giving rise to the *bifid spleen* or *lobulated spleen.*

Atrophy of the spleen is seen particularly in the aged. The typical *senile spleen* is usually small, with a wrinkled capsule, which may be considerably thickened. In the absence of any preceding or associated condition giving rise to pigmentation the organ is usually pale. The

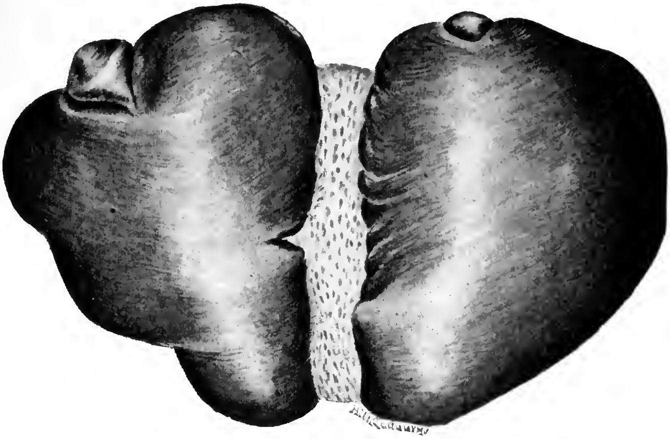


FIG. 230.—SPLEEN CONSISTING OF TWO PARTS JOINED BY FIBROUS BAND.
Each half contains an accessory spleen partly embedded in the posterior margin.

Malpighian bodies and splenic pulp are atrophied, and the fibrous septa are thickened. A closely allied, but by no means identical, condition is found in large spleens with atrophied Malpighian bodies and intensely hyperemic pulp. As a result of fibrous change, a certain amount of contraction may be present. Little is known of **true hypertrophy** of this organ. By some the enlargement of the spleen seen in splenic anemia, Hodgkin's disease, and leukemia is held to be an example of hypertrophy. The increase in size seen in malaria is surely not hypertrophic in character. I would hesitate to regard as hypertrophy the splenic enlargement seen in many infections, infarction, passive congestion, lardaceous disease, cysts, tumors, etc., all of which conditions are clearly distinct from true hypertrophy.

Pigmentary Infiltration.—In chronic malaria[1] the spleen may acquire an enormous size and be intensely pigmented. The viscus may weigh

[1] See Craig, "Amer. Med.," July 25, 1903, p. 145. References to previous papers.

as much as five kilos, or even more. During the earlier infections the spleen is soft, the pulp being almost diffluent and of a dark-brown chocolate color. Thrombosis of the smaller blood-vessels and areas of necrosis are not infrequently present. Later, or after repeated infections, the organ becomes greatly enlarged, firmer, cutting with considerable resistance, as a result of a decided increase in the fibrous tissue ("ague cake"). It may be of a dark slate-color, due to the contained pigment. Histologically, the fibrous septa, the trabeculæ, and the pulp all show an abundant increase, with wide-spread deposit of melanin throughout the connective tissue and pulp. The parasite of malaria may be found in the spleen, and leukocytes containing the organism are not infrequently present.

Lardaceous Disease.—The spleen is large, and may be voluminous, weighing five kilos; it is lighter in color and of higher specific gravity than in health, and contains deposits of amyloid material in sago-grain-like bodies; hence the name, *sago-spleen.* The iodin reaction renders its recognition clear. (See Lardaceous Disease, p. 228.) Under the microscope the lardacein will be seen to occupy the Malpighian bodies; in the earliest stage it probably occurs as an involvement of the arterial branch that the Malpighian body surrounds. There is a form of amyloid spleen in which the infiltration is more diffuse, not in the distinct sago grains, as just described, but involving the pulp and fibrous septa. The chemic reaction is equally well marked, but is more diffuse and less punctiform than in the sago-spleen. (See Plate IV.) As already described, amyloid disease arises in a number of organs almost simultaneously, but the spleen seems to suffer most in the early stage of the wide-spread morbid condition, and, for this reason, any large, rather pale organ should be carefully tested with iodin to differentiate clearly between the enlargements due, for example, to leukemia, and those of amyloid disease. The occasional deposit of hyaline material in the septa, vascular twigs, and reticulum has been regarded as a form of degeneration. It is possibly but a step in the evolution of lardacein.

Calcareous infiltration is seen in the spleen as a result of past necroses, inflammations, or chronic infections. Lime salts are not infrequently deposited in the thickened capsule of chronic capsulitis, which may extend over a considerable area and assume a bony or stone-like hardness. The periphery of quiescent tuberculous areas, cyst-walls, and the cicatrices of old infarcts may show calcareous infiltration.

Acute Splenic Tumor, Splenic Engorgement.—In acute sepsis, and in many of the acute infectious diseases with bacteria or their products circulating in the blood, the spleen seems to become distended with blood; its pulp grows soft and diffluent, and the whole organ becomes edematous and enlarged. This has been considered by some an *acute engorgement,*—an *acute hyperplasia* of the organ,—the result of the accumulation of toxic bodies, and by others a reactionary phenomenon by which the spleen, accessory to other organs, is enlarged in an effort to combat infection. As we are not fully aware of the functions of the spleen or of the organs at work in combating infections, the precise cause of the process can not, for the present, be definitely explained.

The condition has been called *acute diffuse splenitis.* The term engorgement is not the proper one, and the term *infectious splenitis* has been offered as a substitute; the objections to the latter will become apparent when considering splenic infarction.

In addition to the gross changes previously noted, the tension of the capsule may be striking, and during life it may be so great that, with the softening, the spleen may rupture. Postmortem, such an organ is rarely removed without a tear in its capsule through which the abnormally dark, grumous pulp is easily expressed. Such an organ will show, under the microscope, a pulp distended with blood, an enormous number of leukocytes, and red cells, many of the latter fragmented. If bacteria are circulating in the blood, the splenic interstices may be distended by the invaders. The pulp-cells may be found in all stages of their life history—karyokinetic, active, cloudy, granular, and fragmenting; the displaced and softened fibrous network manifests the separation of fibers incident to edema and vascular distention. Commonly, the splenic pulp contains a large number of phagocytes in which may be found bacteria. Some of the phagocytic cells are leukocytes, others are derived from the large endothelial cells lining the pulp sinuses; many of the phagocytes contain erythrocytes. Areas of focal necrosis are practically always present, and in some of these fibrin may be demonstrated. That the condition is not always an infection is shown by the fact that it can be produced by abrin, ricin, and by large doses of sodium nitrate. These considerations, with other clinical and experimental data at hand, would lead us to regard the change as depending upon a toxemia. That all toxic conditions do not bring about the change is shown by its absence in uremia. There can be no doubt that such organs recover; the changes observed in the splenic enlargement of typhoid abundantly establish this fact; but the exact method of repair, of restoration, and of regeneration is not known.

Chronic diffuse splenitis, chronic splenic tumor, *chronic splenic induration,* and *fibroid spleen* are names applied to a condition in which the organ is denser than normal, frequently, although not invariably, pigmented, the capsule thickened and the fibrous tissue of the splenic substance notably increased. The condition is seen particularly in malaria, and includes the manifestation called ague cake, to which reference has been made. Occasionally the splenic enlargements associated with chronic infectious diseases, particularly syphilis and tuberculosis, possess some features of the typical fibroid spleen. Chronic congestion of the spleen due to circulatory deficiency, as in cardiac and pulmonary disease with venous retardation, cirrhosis of the liver, and thrombosis of the splenic vein, frequently gives rise to more or less fibroid change in the organ. Prolapsed spleens contain an excess of fibrous tissue. The gross appearance of the organ is largely determined by the presence or absence of pigmentation and the extent and duration of any associated congestion. When pigmented, the spleen may be brownish, slate-colored, or gray; congestion also renders the organ dark. Typical fibroid spleens are sometimes pale, particularly when pigmentation and congestion are absent. The consistency is always increased, the organ resists incision, and is perceptibly firmer than normal, sometimes quite hard. Histologically the most noteworthy change is the marked increase in fibrous tissue, which may be conspicuous even within the Malpighian bodies. The endothelial cells are often prominent and usually pigmented. From the thickened capsule the broadened fibrous septa and coarser trabeculæ may often be traced to the hilum of the organ. In some cases the hyperplasia involves both pulp and reticulum. These organs are usually softer.

Local splenic fibrosis develops in areas of past infarcts, in the neighborhood of old abscesses and cysts, and around gummata and chronic tuberculomata of the organ. It is possible that some splenic scars are due to the cicatrization of necrotic areas of traumatic origin.

Perisplenitis.—In general peritoneal inflammation the serous covering of the spleen is, of course, involved. By extension of inflammation from some adjacent tissue or viscus—such as the stomach in chronic ulcerative processes, the diaphragm in pleurisy of the left side, perinephric inflammations, and chronic colitis involving the splenic flexure of the colon—the capsule of the spleen may become inflamed and thickened, and may form adhesions. Rarely is this observed as an acute process, but, rather, the results are seen postmortem. The whole of the capsule may be involved (*capsular fibrosis*), or only a small area, *circumscribed capsulitis;* the past inflammation is marked by a layer of formative tissue from 2 mm. to 10 mm. in thickness, rarely thicker, and usually adherent to some adjacent structure—diaphragm, colon, stomach, or posterior abdominal wall. On external examination the white area, if small, may resemble the scar of a past infarct; but on section its purely capsular relation will be apparent. In some instances the newly formed fibrous tissue is piled up in layers, constituting the so-called *lamellar* or *corneal fibroma* of the spleen. In rare instances the new tissue is cartilaginous. Sometimes the capsular inflammation and its associated thickening extend along the fibrous septa downward into the spleen. When the capsulitis has been uniformly disseminated over the whole organ, the mass, before section, may not resemble the spleen: during operation it has been mistaken for a tumor; its position, relations, and attachments during life should prevent such an error, and an incision postmortem quickly exposes the characteristic splenic parenchyma. It is possible that the uniformly thickened capsule might, by contraction, lead to atrophy of the splenic structure, but it is not known that such a process ever occurs to a sufficient extent to involve the function of the organ.

In cirrhosis of the liver with obstructed portal circulation, in prolapsed and wandering spleens, in cardiac or pulmonary disease associated with venous engorgement, and during or after thrombosis of the splenic vein, more or less **passive congestion of the spleen** occurs. The organ becomes large, soft, sometimes semifluctuating, and nearly always dark in color; later, it may be rather fibroid. The condition is analogous to the changes in the cyanotic kidney. There is usually a decided increase in the fibrous tissue, distended blood-vessels, edematous and rather fluid pulp, and considerable pigmentation.

Hemorrhage into the splenic pulp occurs in nearly all infections that prove fatal, and is, therefore, usually demonstrable in any spleen showing engorgement of the kind described on page 434. As a result of injury during delivery, and sometimes in the infections that follow, splenic hemorrhage is seen. It also occurs in the new-born as a manifestation of congenital syphilis. The hemorrhage may be diffuse or focal. Focal hemorrhages are commonly multiple, and vary in size from 1 mm. or 2 mm. to accumulations as large as an orange. Little is known of the changes that take place in areas of hemorrhage occurring in patients who recover. It is probable that the blood is absorbed, and that more or less fibrous tissue results. Marked increase in the

contained pigment is practically always present, but is usually not sufficiently circumscribed to identify the area positively.

Splenic Infarction.—In no organ more clearly than in the spleen are to be seen the results of lodged emboli. The vessels to the spleen are characteristically terminal, and their distribution and ending in the splenic pulp are such that no embolus is likely to traverse the organ without being arrested. *Simple emboli* induce infarcts, distinctly conoid or irregular; on section, wedge-shaped; with, in the early stages of the process, an elevated surface; in color purplish (*hemorrhagic infarcts*), black, or of a combined tint; soft at first, later firm, and, again, after coagulation has terminated in liquefaction necrosis, soft, semifluid, or even cystic in consistency.[1] Later, if not too large, organization and cicatricial tissue formation convert the mass into a pale and eventually white cone of scar tissue extending more or less deeply into the parenchyma of the organ; sometimes such a scar extends to the hilum, almost dividing the organ into two parts. In other cases the infarct contains but little blood; it does not become purplish or black, as in the foregoing, but is of a light pink, pinkish-white, or whitish hue, and hence is called *anemic* or *white infarct*.[2] There is the same coagulation necrosis, followed by liquefaction necrosis, and probably the result is the same as in the area of the hemorrhagic infarct. The number of infarcts may be so great as to preclude counting; as a rule, more than one are present. While usually on the surface, they are not always superficial, and, while most frequently the area involved is cone-shaped, the blending of a number of infarcts may offer so misleading a picture as to require careful study for positive identification

Infected emboli quickly produce an entirely different picture. Probably, in the early development of the infarct, the appearance is the same; soon, however, the area involved is converted into an abscess, and as such abscesses are usually multiple, the spleen becomes studded with small pus cavities, or may show, by confluence, one or more of much larger size. It is well to remember that the soft, juicy, splenic pulp, with its open-mouthed blood-vessels, may contain a pus in which leukocytes, necrotic tissue, and extravasated blood are so commingled that the resulting substance lacks the macroscopic appearance of pus.

Splenic abscess[3] may also arise from direct injury of the spleen and from extension of suppurative processes from adjacent organs, such as perforating ulcer of the stomach, and at times without any discernible cause. The occurrence of splenic abscess in typhoid fever and other acute processes must be looked upon as resulting from pyogenic infection of an area of necrosis, itself caused by the activity of toxins circulating in the blood. It is admitted, of course, that the typhoid bacillus might possibly induce suppuration without the presence of pyogenic cocci. Actinomycotic and gummatous lesions occasionally suppurate. Many splenic abscesses are preceded by malaria. Splenic suppuration may follow pelvic or appendicular abscess. Abscess of the spleen may be single or multiple. Embolic abscesses are usually, although by no means always, multiple. Abscesses resulting from trauma and from

[1] See Fig. 152, p. 282.

[2] See Infarction, p. 281.

[3] Pince, Thèse, de Paris, 1903. Stavely, "Annals of Surgery," June, 1903, p. 866. Spear, "Jour. Amer. Med. Assoc.," Aug. 1, 1903, p. 304.

direct invasion of the splenic tissues are commonly solitary. An abscess may be superficial or deep; its shape is largely dependent upon the cause; embolic abscesses are usually more or less irregularly conic, and traumatic abscesses are commonly ovoid or spheric. The pus from splenic abscess is usually dirty-red or chocolate color and frequently contains shreds or necrotic masses of splenic tissue. When the suppurative lesion approaches the surface, a perisplenitis results. This may attach the spleen to the abdominal wall or to one of the hollow viscera. An abscess may rupture into the peritoneal cavity, into some adjacent hollow viscus, or, where the process is limited, inspissation and encapsulation occasionally occur.

Thrombosis of the splenic vein, while rare, may occur, giving rise to edema and distention of the organ resembling the congested spleen; there is commonly more edema, and, as the process is acute, less fibrous tissue is present. The thrombus may be an extension backward from the portal vein, or, arising in the splenic vein, may extend into the portal.

Gangrene of the Spleen.—The wandering spleen may, by twisting its pedicle, cut off the blood-supply and blood exit; the poisons produced by the disorganization of the splenic tissue favor the migration of bacteria from the adjacent alimentary canal, and, by this infection, the dissolution of the organ terminates in gangrene. The author has known two cases, undiagnosticated during life, and both found with evident infection postmortem. Gangrene of the spleen may also follow embolism, thrombosis of the splenic vein, pressure by neoplasms or penetration of the organ by necrosing processes begun in some contiguous tissue.

The term **splenomegaly**[1] has been applied to a number of conditions having in common a splenic enlargement not associated with a recognizable type of infectious disease, and not including the enlarged spleens of leukemia or the familiar form of Hodgkin's disease. Those cases in which the enlargement is accompanied by anemia have been called **splenic anemia ;** in these the organ is conspicuously enlarged, the fibrous tissue somewhat increased, and there is marked endothelial hyperplasia. Herzog suggests that the proliferating endothelial cell secretes some erythrolytic substance through the activity of which the red blood-cell destruction is accomplished. An interesting feature of these cases is the prompt recovery following splenectomy. In another group of cases the spleen is enlarged and may weigh 3 kilos; the lowest weight recorded

[1] Banti, "Ziegler's Beiträge," 1898, xxiv, p. 21; also "Rif. Med.," March 1 and 5, 1901. Muir, "Jour. of Path. and Bact.," Feb., 1901. Herzog, "Chicago Path. Soc.," March 11, 1901. Brill, "Amer. Jour. of Med. Sci.," April, 1901, p. 377. Rolleston and Jones, "Chir. Soc. of London," Feb. 28, 1902. Field, "Amer. Jour. of Med. Sci.," March, 1902, p. 405. Azzurrini, "Lo Sperimentale," 1902, Nos. v, vi. Emile-Weil and Clerc, "Arch. Gen. de Méd.," Nov., 1902. Morse, "Boston Med. and Surg. Jour.," May 28, 1903. Osler, "Amer. Jour. of Med. Sci.," Aug., 1903, p. 187. Carpenter, "Brit. Med. Jour.," Aug. 29, 1903, p. 463. Quenu and Duval, "Revue de Chir.," Oct. 10, 1903, p. 444. Levison, "Annals of Surgery," Nov., 1903, p. 671. Borissowa, "Virchow's Arch.," 1903, Bd. 172. Osler, "Brit Med. Jour.," Jan. 16, 1904, p. 121. Türk, "Wien. klin. Woch.," Feb. 11, 1904, p. 153, and Feb. 18, 1904, p. 189. Weber and Watson, "Clinical Soc. of London," March 11, 1904. Stürmer, "Brit. Jour. of Obst.," Oct., 1904. Gilbert and Lereboullet "Soc. de Biologie," Nov. 12, 1904. Weintraud, "Zeit. f. klin. Med.," vol. 55. Brill, Mandlebaum and Libman "Amer. Jour. of Med Sci.," March, 1905, p. 491.

is over 600 gm., and the average of the reported cases over 1500 gm.; sooner or later the condition is followed by cirrhosis of the liver. The affection is called **Banti's disease,** after its discoverer. By some observers the splenic enlargement that follows hepatic cirrhosis is classed with splenomegaly. According to Azzurrini, the changes in the organ are identical with those resulting from other forms of stasis affecting the spleen. The veins and sinuses are dilated, the follicles wasted, and the erythrocyte content of the organ is enormously increased. Under the name of **primitive splenomegaly** or **primary epithelioma** of the spleen has been described a condition in which the organ is markedly enlarged, firm, and contains white or yellowish-white areas resulting from hyperplasia of the endothelial cells and some increase in the fibrous tissue. The term epithelioma, sometimes applied, is misleading, and should be replaced by endothelial hyperplasia; as the evidence of tumor formation is not convincing, the name endothelioma is also objectionable. In still another group of cases the splenic enlargement is associated with polycythemia and proportionate increase in the hemoglobin—a condition to which reference is made on page 411. In this condition there is marked hyperplasia of the pulp and endothelial cells, and, like the other forms of splenomegaly, is not explained by any facts with which we are at present familiar. In still another group of cases the splenic enlargement is clearly of a neoplastic type with definite tumor formation in the parenchyma of the organ. These cases should not be included with the forms just mentioned.

Leukemia and Pseudoleukemia.—In these diseases the spleen is often much enlarged, pale or bright red, with tense capsule, and not uncommonly with adhesions to the adjacent organs. The largest spleens are found in myelogenous leukemia, in which disease the weight of the organ may approach 8 or 9 kilos. Accessory spleens usually show enlargement. The density of the organ seems to be dependent more upon the duration of the process than upon the kind of leukemia. Infarcts are frequently present, and are often of different ages. In some cases the Malpighian bodies stand out as lightly colored nodules on the incised surface, so clearly enlarged as to be most prominent features; in other cases the cut surface is uniform. Under the microscope the hyperplasia seems to involve the entire splenic parenchyma as a lymphoid cellular growth, either shown, as previously indicated, by overgrowth of the Malpighian bodies and pulp, the former in excess, or of both structures without apparent differentiation. In leukemia the splenic enlargement may be largely due to the intercalation of leukocytes, the added white cells being of the same kind as those found in excess in the blood. In other cases the spleen contains definite tumor-like masses, sometimes called lymphoid growths. Such tumors vary in size from purely microscopic bodies to nodes two or three centimeters in diameter; they sometimes project on the surface of the spleen. (For blood condition in leukemia and pseudoleukemia see pp. 424 and 430, and table on pp. 428 and 429.)

Rupture of the Spleen.[1]—As a result of violence—either directly ap-

[1] Eisendrath, "Jour. Amer. Med. Assoc.," Oct. 25, 1902, p. 1032; also "Annals of Surgery," Dec., 1902. Editorial in "Lancet," Sept. 26, 1903, p. 895. Craig, "Med. News," April 23, 1904, p. 780. Davys, "Brit. Med. Jour.," May 7, 1904, p. 1077. Auvray, "Soc. de Chir.," Nov. 9, 1904; also "La Presse Méd.," Jan. 11, 1905, p. 17.

plied, as by a blow or fall, or transmitted, as by the sudden arrest of the body, as in falling from a height—the spleen may rupture; when enlarged, the most trifling accident may be followed by laceration, and, when intensely engorged or softened, as in infectious diseases, including malaria, rupture may occur without recognizable trauma—so-called *spontaneous rupture.* The resulting hemorrhage is likely to be severe, but is not invariably fatal, and in rare instances, with small stellate tears, a clot may form and the organ may undergo repair by the subsequent formation of cicatricial tissue. Rupture may occur in areas of septic infarction, splenic abscesses, and cysts. In addition to true rupture, which necessarily involves the capsule, **interstitial** or **subscapular lacerations of the spleen** are occasionally observed; these may be attended by circumscribed or diffuse hemorrhages into the parenchyma and consequent areas of necrosis, and are sometimes followed by cyst formation—so-called **metaclastic cysts** of the spleen; some writers include with these the loculated parasplenic hemorrhages that sometimes result from injury of the organ. According to Brunswic-le-Bihan,[1] the metaclastic cysts may contain eight to ten liters of greenish, sterile fluid abounding in leukocytes and normal and altered erythrocytes.

Chronic Infections of the Spleen.—The most frequent of these is tuberculosis. (Plate IX.) According to Auché,[2] there are ten recorded cases of primary splenic tuberculosis; in nine of these the lesions were chronic caseous, fibrocaseous, or calcareous in type. Secondary tuberculosis of the spleen may be acute or chronic. In acute general miliary tuberculosis there is practically always an almost uniform invasion of the splenic tissues with typical miliary tubercles located near the arteries, in the pulp, in the Malpighian bodies, or even in the capsule of the organ. In chronic tuberculosis of the spleen the organ contains one or more, rarely many, caseous or caseocalcareous areas 5 mm. to 5 cm. in diameter and often encapsulated. The smaller nodules may be completely cretaceous, constituting one form of the so-called splenic calculus.

Syphilis of the spleen occurs in two forms—*congenital* and *acquired.* The congenital type may be manifested in one of two ways: (1) Diffuse splenic fibrosis with some enlargement, which, however, is not usually marked, although Ziegler records an instance in which the enlarged spleen weighed 100 gm. at birth; according to Marfan, the most constant lesion of hereditary syphilis is enlargement of the spleen. (2) In other cases true gummata are found. The splenic lesions of *acquired syphilis* vary with the stage of the disease during which the organ is involved. In the earlier stages of syphilis the spleen may participate in the hyperplasia found in a number of the blood-making organs, especially the lymphoid tissue; in the late secondary or early tertiary period a diffuse fibrosis is not infrequently present; later, the characteristic lesion of tertiary syphilis—the gumma—is occasionally seen. Commonly, the lesion is solitary, but in very rare cases two or more gummata may be found. The size varies greatly; the mass is spheric or oval, of a pearly-white or grayish-white color, and is sometimes translucent, particularly at the margin. Like chronic tuberculosis, the masses are sharply defined at their margins, but, unlike the tuberculous nodule, caseation is not a characteristic.

[1] "Revue de Chir.," Nov. 10, 1904, p. 648.
[2] "Jour. de Méd. de Bordeaux," June 2, 1901.

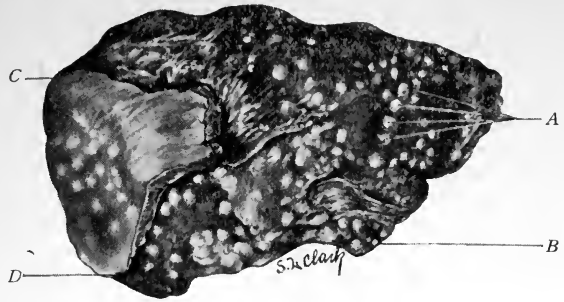


FIG. 1.

SPLEEN. CHILD AGED 2 YEARS. SUBACUTE MILIARY TUBERCULOSIS. (Two-thirds natural size.) The appearance in this case strongly indicated that all the tubercles were not of the same age.

A. Older distinctly caseous conglomerate tubercles. *B*. Two recent miliary tubercles. *C* to *D*. Diaphragm through which relatively large caseous conglomerate tubercles can be seen.

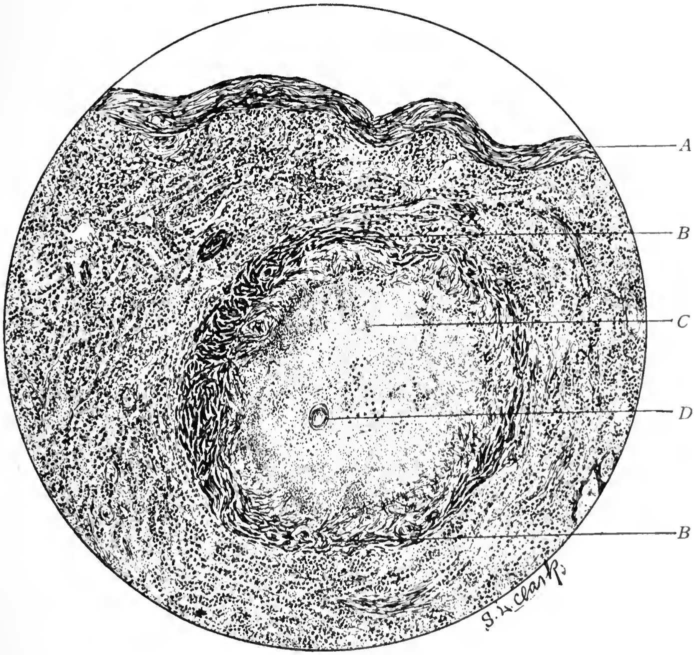


FIG. 2.

SPLEEN. QUIESCENT CASEOUS TUBERCULOSIS; ADVANCED ENCAPSULATION OF CASEOUS MASSES. (Two-thirds natural size.)

A. Capsule of Spleen. *B B*. Fibroelastic capsule of necrotic area. *C*. Area of caseation necrosis. *D*. Thrombosed vessel.

Leprosy of the spleen manifests itself by the occurrence of nodules of granulation tissue containing lepra cells loaded with the bacilli in quite characteristic clusters.

Actinomycosis of the spleen occasionally occurs; with the development of the actinomycotic node. suppuration usually ensues, engendering an actinomycotic abscess of the organ.

Tumors of the Spleen.—Splenic tumors are not common. The primary tumors in an otherwise normal spleen are, of course, connective-tissue neoplasms; of the adult or typical series, osteoma, fibroma, and lymphangioma are occasionally observed; cavernous hemangiomata, which may be multiple, are sometimes encountered.[1] Sarcoma is less rare. Secondary tumors are more frequent than the primary growths, and as sarcoma travels by the blood-stream more frequently than carcinoma, it is the usual secondary neoplasm of the spleen. Cancer, however, does occur.

Cysts[2] of the Spleen.—Cysts are found in the spleen oftener than primary neoplasms. They may result from the encapsulation of massive infarcts, or areas of necrosis resulting from injury,[3] which, by reason of their size, have failed to organize and have not been absorbed. Some splenic cysts are lymphangiomata. The usual cyst is, however, of parasitic origin (hydatid), and may attain considerable size; rarely, the parasitic cysts of the spleen are multiple.

[1] See Pumpelly, "Med. Record," Jan. 9, 1904, p. 51, and Thiele, "Virchow's Archives," Nov. 3, 1904, p. 296.

[2] Otto, Inaug. Diss., Tübingen, 1904

[3] See Rupture of Spleen

CHAPTER III.

LYMPH-NODES [1]

The lymph-glands, or, more appropriately, the **lymph-nodes,**[2] are structurally composed of a peculiar form of cell which, when massed together, constitute lymphoid tissue; these, in the node, are retained in place by a reticulum of connective tissue. The lymph-node lies loosely in the connective tissues, and, in addition to its blood-supply, receives through its capsule the afferent lymph-vessels, draining lymph from the area beyond; after passing through the node the lymph finds its exit by way of the efferent vessel, eventually reaching the blood through the vein into which the lymph-vessel empties. The capsule of the node is composed of fibrous tissue, with some unstriped muscle-fibers; from the capsule run septa that converge at the hilum, dividing the node into follicles. Each follicle is made up of a reticulum, scaffolding, or sponge-like network of connective tissue, in the spaces of which are lodged the lymphoid cells; toward the periphery of the ovoid follicle the lymphoid cells are smaller than in the center, in which many of the larger form show active karyokinesis. The lymph, in passing through the node, is in intimate contact with the cells of the parenchyma, and in this way is probably altered in composition and cellular contents; at the same time the node structure is exposed to whatever deleterious influences the lymph, in its return to the circulation, may bring. It will thus appear that the nodes may be influenced by the blood brought to them and by the lymph of the area drained.

The **hemolymph-nodes**[3] occupy a histologic and probably a functional position intermediate between the ordinary lymph-nodes and the spleen. Our knowledge concerning these structures is a comparatively recent acquisition, and we are as yet unfamiliar with many phases of their pathology. Warthin has shown that they increase in size and that new nodes are developed after splenectomy. In pernicious anemia the blood-sinuses dilate and the endothelial cells engulf erythrocytes and frequently become pigmented; in some cases these structures show a marked hyperplasia.

Lymphoid Atrophy.—In the old this process is normal. It may be a *metaplasia*, the node being more or less replaced by adipose tissue.

[1] The examination of the lymph-nodes during a postmortem is regional: that is, the glands of an area are examined with other organs of the region, so that the consideration of their special pathology at this point, near the spleen, is due to the intimate association of their lesions with those of the spleen rather than to any special propriety of considering them at this time.

[2] For recent study of the histology of lymph-nodes, see Bunting, "Jour. of Anat. and Physiol.," 1905, vol. xxxix, Part 3.

[3] Warthin, "Amer. Jour. of Med. Sci.," Sept., 1902, p. 674; "Trans. Chicago Path. Soc.," 1902, vol. v, No. 8, p. 151; also "Proceed. Path. Soc. of Phila.," Dec., 1903, n. s., vol. vi, No. 10, p. 12. Dayton, "Amer. Jour. of Med. Sci.," March, 1904, p. 448. Lewis, "Jour. of Anat. and Physiol.," 1904, vol. xxxviii, Part 3.

Such nodes are usually firmer and paler than normal, but may be pigmented and dark.

Pigmentary Infiltration.—Whatever pigment the lymph may find in the tissue of the area drained is brought to the node, and may be deposited (p. 231). Thus, in the removal of blood extravasated into the connective tissue, the coloring-matter gathered by migrating cells is brought to the node by the afferent vessels and deposited. In anthracosis—indeed, in all forms of pneumoconiosis—the pigment from the lung is carried to the adjacent lymph-nodes, where it may be deposited in such quantities as to render the structure brown, gray, slate-colored, or even black. Some of the infiltrated material, as certain calcium salts, may be removed; other solid or insoluble bodies may remain as a permanent part of the node. The infiltrated material may induce a chronic indurative inflammation and the production of fibrous tissue, thus rendering the node firmer, larger, and less efficient in physiologic activity than normal. Whether or not normal lymph-nodes are likely to be invaded by calcareous matter can not be definitely settled, but certainly an inflamed or infected gland is exceedingly subject to the deposit of lime in its interior. Bone is sometimes found in lymph-nodes[1] and in the tonsils; in the latter structures Ruckert believes that the change results from inclusion of fetal cartilage during development. The bone found in the lymph-nodes may be due to a true metaplasia of the connective tissues, but is usually associated with tuberculosis of the affected structures. It may be superficial (capsular) or interstitial.

Lardaceous disease affects lymph-nodes as it does other tissues of the body. At times it would seem that there may be lardaceous deposits in the nodes of an area without manifest general deposition in other tissues. This is said to arise as a result of the lymph bringing to the node a material, or irritant, which leads to the change, and which, being arrested in the node involved, permits the other tissues to escape. (See Amyloid Disease, p. 227.)

Of the degenerative changes in lymph-nodes but little can be said. They are usually due to irritants brought to the nodes, and occupy positions of secondary importance. It would seem, however, that **hyaline degeneration,** and possibly **colloid change,** may occur in lymph-nodes without any apparent or discoverable antecedent disease. Both affect the vessels and reticulum and are rarely marked.

Infections of Lymph-nodes.—These structures, probably more than any other tissue, possess a remarkable susceptibility to the influence of bacteria or their toxic products. There is hardly a known infection, from bubonic plague, which seems to explode its virulence on the lymph-nodes, to the most chronic infection, such as leprosy, which does not either directly or indirectly modify the structure and function of the lymphoid tissues. Edsall[2] has shown that even in typhoid fever the lymph-nodes of the axilla, neck, or groin are occasionally perceptibly enlarged. The change in most cases is an inflammation, a *lymphadenitis*, which may extend to the tissues around and give rise to a *perilymphadenitis*. As to time, the process may be fulminatingly acute, or may extend over months or even years.

[1] See Lubarsch, "Virchow's Arch.," 1904, Bd. 177, p. 371. Also Ruckert, ibid., 387. Both articles also deal with a similar change in the tonsils.
[2] "Amer. Jour. of Med. Sci.," April, 1904, p. 599.

In the **lymphadenitis** arising from the ordinary infections, such as those produced by the pyogenic bacteria, the appearance of the node is more or less modified according to the stage of the disease. At first it is swollen, tense, and tender, and the obstruction to the passage of fluid through the node may be evinced by a surrounding or overlying edema, or a swelling in the tissues of the area drained. On section, the surface is gray, grayish-white, or pink, or, rarely, there may be enough contained blood to give the incised tissue a darker hue. In a node not previously indurated the parenchyma is soft, and may be diffluent. Under the microscope the lymph-channels are distended by leukocytes, and commonly contain fibrin; in the follicles areas of coagulation necrosis, containing fragmented endothelium and leukocytes, are usually conspicuous. Later, the necrosis extends beyond the follicles, involving the septa, and eventually the capsule and circumglandular tissues. Such an inflammatory and necrotic mass constitutes a **bubo.** Buboes are common in the groin during infectious lesions of the genitalia and superficial infections of the lower extremity, in the axilla from similar lesions affecting the arm, hand, or mamma, and in the neck when the initial process is in the superficial tissues of the scalp, face, mouth, or pharynx. One must not forget possible unusual lymphatic distribution: for example, cases in which involvement of the supraclavicular nodes follows disease of the breast, the corresponding axillary structures escaping.

Suppuration of the lymph-nodes fails to occur in many infections, particularly those in which the infecting organism does not possess the faculty of pus production. In these cases there is necrosis of the lymphoid tissue, with corresponding interference with function. Thus, in diphtheria the toxins absorbed from the involved area give rise to edema of the lymph-nodes, coagulation necrosis, and periadenoid serous infiltration; these changes probably lessen the phagocytic, bactericidal, or other protective powers of the lymphoid tissues to such an extent as to permit of suppuration should pyogenic bacteria be carried into the node. The somewhat dense capsule of lymph-nodes permits the occurrence of a rather prolonged intraglandular inflammation without infection of the surrounding tissue; such a battle between the invading organism and the gland-cells may terminate in a victory for the latter, or in a drawn battle, in which case periadenoid induration and subsequent dense fibrosis, with possible calcareous change, may so surround the area of danger as permanently to include it as a "healed-in" focus. It is a limitation of this type that occurs in tuberculosis, and, though less commonly, in actinomycosis, glanders, and other infections that attack the lymphoid tissues.

The slow continuous or interrupted delivery to the lymph-nodes of irritant bodies, such as may be derived from some permanent area of infection or from dust—as in pneumoconiosis when solid particles are being constantly brought to a node—induces a more or less subacute or chronic productive change, during which new fibrous tissue may be formed in and around the node, constituting **adenitis chronica** or **periadenitis chronica,** or the two lesions combined.

Of the chronic infections occurring in lymph-glands, tuberculosis and syphilis are the most important, although leprosy may involve the lymphatics.

Tuberculous lymphadenitis,[1] the *scrofulous lymphadenitis* or *scrofula* of the older writers, arises from invasion of the lymph-nodes by the bacillus of tuberculosis brought to the gland by the lymph or blood. That it is usually lymphogenous can not be doubted; but this would not account for those occasional cases, really rare, apparently no system of glands in the body escaping, and in which affected tissues develop tuberculosis at so nearly the same time as to preclude the belief that the initial lesion was in any one area. It may be possible that these cases are general infections directly by the blood: that is, tubercle bacilli carried throughout the organism reached the lymph-spaces, and from these were transferred to the lymph-nodes. Whatever may be the cause, undoubted cases of almost universal lymphatic tuberculosis occur. The frequent form of the affection is **regional tuberculous lymphadenitis;** in this form the disease attacks some chain of lymph-nodes in such a manner as to indicate a fairly clear source or route of infection. Under this head come *cervical*, *mediastinal*, *mesenteric and retroperitoneal*, *axillary*, and *inguinal lymphadenoid tuberculosis.* The route of invasion, or, rather, the portal of entry, can often be surmised, and, although rarely, at times demonstrated. A mucosa weakened by inflammation is usually the vulnerable tissue through which the infection occurs; thus, tuberculosis of the cervical lymph-nodes is observed to follow catarrhal processes affecting the nose or throat or inflammatory lesions in the mouth. The frequency of mesenteric tuberculosis in bottle-fed children, in whom indigestion and catarrhal lesions pave the way for the entrance of the bacillus of tuberculosis (admittedly not an infrequent milk contaminant), is largely explained by admitting the increased permeability of an already diseased mucosa. The frequency of tuberculosis of the mediastinal nodes following influenza is similarly explicable. As already stated, the point of entry of the bacillus can sometimes be more or less accurately determined. Senn reports a case in which a nontuberculous girl wore the earrings of a tuberculous sister, and later developed a local tuberculous outbreak. The author saw a case of axillary tuberculosis follow a wound made by a corset steel on the outer margin of the breast in a young girl nursing a sister in an advanced stage of tuberculosis of the lungs; the glands were removed, and no further evidence of tuberculosis has been observed.

Cervical tuberculous lymphadenitis is clearly the result of infection from the oral and pharyngeal cavities. Halle found that in 3161 children with enlarged cervical glands, 2334 had carious teeth; and of these, 1646 corresponded in location with the enlarged glands. Odenthal, among 987 children, found decayed teeth in 429; 424 of these had enlarged lymph-nodes. Halle demonstrated that if cavities in the teeth of dogs be packed with Prussian blue and cemented, the

[1] Finkelstein, "Vratch," June 2, 1901. Sailer, "Phila. Med. Jour.," April 5 and 12, 1902. Mitchell, "Bulletin of Johns Hopkins Hospital," July, 1902. Roughton, "Lancet," Oct. 18, 1902, p. 1032. Dowd, "Annals of Surgery," 1903. Carriere, "Zentralbl. f. innere Med.," July 11, 1903, No. 28. Macfadyen and Macconkey, "Brit. Med. Jour.," July 18, 1903, p. 129. Weill and Pehu, "Lyon Méd.," Aug. 9, 1903, p. 228. Morf, "N. Y. Med. Jour.," Aug. 29, 1903, p. 410. Hand, "Proc. Phila. Path. Soc.," March, 1903, p. 132. Westenhoeffer, "Berl. klin. Woch.," 1904, Bd. xli, Nos. 7 and 8. Freeman, "N. Y. Acad. of Medicine," April 7, 1904. Painter and Erving, "Amer. Med.," Sept. 24, 1904, p. 539.

pigment may, in from two to three days, be present in the nearest lymph-nodes. Dieulafoy and others have shown that tonsils—frequently without evidence of tuberculosis—may contain the bacillus, and that the organism often is present in adenoids.[1] All observers are agreed that glandular infection of this type is a disease of childhood and adolescence; Finkelstein found it in 456 cases; 329 of the patients were between ten and twenty years of age. In Hand's series of 332 autopsies on children, 115 had tuberculosis; of these, infection appeared to have been primary in the bronchial glands in 75, in the mesenteric nodes in 10, and in the tonsil in 1; in the remainder it was not possible to say at what point infection probably occurred. Mitchell states that a family history of tuberculosis is present in about half the cases, and that less than five per cent. of those affected present evidence of pulmonary involvement

Morbid Anatomy.—The studies of Walsham clearly establish that neither macroscopically nor microscopically is it possible in all cases to recognize the tuberculous nature of the affection; the anatomic character of the lesion is so varied that nothing short of demonstrating the bacillus is trustworthy. The condition long known as lymphoid or endothelial hyperplasia of the lymph-nodes is, in many if not in all cases, a manifestation of tuberculosis; the histologic tubercle is frequently absent and often there is no cell accumulation resembling such a structure. In these cases the endothelial cells of the lymph-sinuses are found proliferating and the mononuclear elements greatly increased; sometimes fibrin can be demonstrated and areas of necrosis are often present. In such cases the diagnosis of tuberculosis must rest upon the identification of the bacillus. In other instances the diagnosis may readily be made. The affected nodes are very much enlarged, swollen, and, at first, not attached to the intervening and surrounding tissues; the capsules are thin and tense. On incision, early in the case, the node is more or less hyaline, translucent, and succulent; scattered throughout its structures tubercles in different stages of development and in all degrees of necrosis and degeneration, may be seen; later, these bodies may become fibroid, caseous, or calcareous. In the mean time the node shrinks in size, grows fibroid, and develops a dense and thickened capsule. Such nodes as the last-described represent a "healed-in" tuberculosis, or *quiescent tuberculous lymphadenitis.* In less favorable instances the process of caseation involves the whole node; eventually, a periadenitis is induced, and the node becomes adherent to contiguous structures; masses of such structures may coalesce. These either break down singly or a number caseate at once, giving rise to a tuberculous abscess, the contents of which are free from pyogenic bacteria. In a small percentage of the cases pyogenic bacteria may have gained ingress either with the tubercle bacilli or as a secondary infection; under such circumstances the inflammation will be attended by more marked systemic phenomena and the suppurative changes will be more conspicuous. On the whole, it may be said that tuberculosis of the nodes has a tendency toward the conservative processes of sclerosis and limitation, and that general dissemination is not likely to occur; exceptions to this statement are not infrequent.

[1] See Paths of Infection in Tuberculosis, p. 148.

The histology of this type of lymphadenoid tuberculosis is usually quite characteristic and permits a reasonably accurate diagnosis even when the bacillus cannot be demonstrated. With the deposit of the tubercle bacilli in the lymph-node the evidence of infection begins. There is quickly developed an epithelioid accumulation resulting from proliferation of the endothelial cells of the lymph paths; to these are added a few polymorphonuclear leukocytes, which, with the accumulation of mononuclear cells apparently of hemal origin, constitute the anatomically mature tubercle. A number of these become confluent, and caseation occurs, followed by local diffusion involving the whole node and later a periadenitis that binds the nodes of the area together. The infection may spread to the circumadenoid tissues, and eventually, by the route of least resistance, may reach the skin. During this time it is possible that some of the bacilli may have passed the node and assured further extension of the process by a second incursion through the lymph-stream. (See Tuberculosis, p. 153.)

The course just described may be arrested at any point. The bactericidal action of the lymphoid structures, including the leukocytes, may terminate the process by a victory for the inhibiting forces, the bacilli succumbing or becoming so surrounded by a protective cordon of leukocytes as to limit the lesion to the area involved, or, possibly, to a single node, or even to a part of a node. This "healing-in" of the affected tissues does not represent a cure, but merely a quiescent infection, which may, when the protective power is weakened by some secondary or intercurrent malady, break out anew. The relation of these glands to the production of miliary tuberculosis is discussed on page 154. Caseous nodes may discharge into serous or other cavities; Metcalfe[1] reports an instance of sudden death due to rupture of a caseous node into the trachea just above the bifurcation

Syphilitic Lymphadenitis.—The nearest anatomic lymph-node draining an area in which there is an initial lesion of syphilis manifests, as a rule, a reaction to the invasion, which is quickly followed by swelling of contiguous nodes, and eventually, in the vast majority of cases, by hyperplasia of the lymphadenoid tissues at large. This initial or primary glandular involvement seems to be almost purely a proliferative change in the cells of the lymphoid follicle and further blocking by leukocytes. The change is usually transitory, and disappears in a few days under treatment, and, often, in a few weeks without. In addition to this primary involvement of the nodes gummata may be present in an active stage of development, or gummatous changes represented by atrophied, cicatrized, or caseous areas of a practically cured tertiary glandular lesion.

Hodgkin's disease,[2] lymphadenia, lymphadenoma, lymphosarcoma, progressive lymphadenoid hyperplasia, malignant lymphoma, simple

[1] "Lancet," May 25, 1901.

[2] Reed, "Johns Hopkins Hospital Reports," 1902, vol. x, p. 133. Hitschmann and Stross, "Deut. med. Woch.," May 21, 1903. Simmons, "Jour. of Med. Research," 1903. Tüerck, "Wien. klin. Woch.," 1903, No. 39. Longcope, "Bulletin of the Ayer Clinical Laboratory of the Pennsylvania Hospital," Oct., 1903, No. 1. Falkenheim, "Zeit. f. klin. Med.," 1904, lv. Gamasaki, "Zeit. f. Heilk.," 1904, Bd. xxv, Heft 7, p. 269. Hutchison, "Lancet," 1904, vol. i. Shaw, Practitioner," Oct., 1904, p. 517. Wells and Maver, "Amer. Jour. of Med. Sci.," Nov., 1904, p. 837.

adenia, pseudoleukemia, and other more or less synonymous terms, have been applied to a peculiar form of lymphoid change in which one or more of the lymphadenoid tissues of the body are involved, including not only the lymph-nodes, the spleen, and the tonsils, but even the lymphoid tissues of the various mucosæ. There can be no doubt that a number of conditions have been included in this group, but careful study by modern methods, and particularly the investigations of Reed, Simmons, and Longcope, render it possible to recognize a fairly definite anatomic picture, properly to be identified as distinct from neoplasms affecting the lymph-nodes and not due to any form of infection with which we are at present familiar.

FIG 231.—HODGKIN'S DISEASE.—(*From a photograph taken a few weeks before the death of the patient from mediastinal involvement.*)

The lymphatic enlargement in both axillæ is shown, as well as the unusual collar-like glandular involvement in the neck. The nodes of the left axilla show the tuberous or nodular character of the enlargement, as they have not as yet matted together. In the right axilla the individual nodes are not easily outlined. The right arm is swollen from pressure on the axillary vein, and possibly from obstruction to the lymph flow through the involved nodes. At postmortem examination the mediastinal, retroperitoneal, mesenteric, and inguinal lymphatics were all found to be involved. (Patient of Professor J. C. Wilson, in the wards of the Jefferson Medical College Hospital.)

The glandular enlargement follows no law; each case differs from all others. As a rule, the first nodes to enlarge are the cervical. A cluster of lymph-nodes may become prominent in a comparatively short time, may remain quiescent sometimes for months, and then suddenly take on renewed activity. Following the cervical nodes in order of frequency come the axillary and inguinal glands. In extremely rare cases the disease begins in, and remains restricted to, some group of internal nodes, such as the mediastinal, retroperitoneal, or bronchial; later in the affection usually all these groups are implicated Some of the glands may contain caseous areas accurately circumscribed, and probably the result of a past, or superimposed, tuberculous infection. The disease, however, bears no relation to tuberculosis—association of the infection is mentioned only to indicate the possibility of combined lesions. The process is not restricted to the lymph-nodes properly so called, but the lymphoid tissues throughout the body may manifest a certain amount of involvement, new areas of lymphadenoid tissue sometimes develop. The splenic changes have already been considered. (See p. 439.) The adenoid tissue of the alimentary canal becomes conspicuous, and lymphoid growths in the liver and pancreas are occasionally found. The thymus and thyroid bodies and the suprarenal capsule may be involved; rarely, lymphoid growths occur in the central nervous system.

The enlarged nodes are white or grayish-white, and are either firm or soft, depending upon the rapidity of their growth; in rare cases there may be evidence of necrosis in the interior. As a rule, they remain distinct until reciprocal pressure or peripheral growth has coalesced them, and not until they have attained considerable size do they show evidence of marked periadenoid extension; to this rule there are notable exceptions, and occasionally, in a group of glands, many differences in consistency, in color, and in evidences of infiltration may be present.

Histologically the growths from different cases rarely present identical changes. There runs, however, through them all, certain conspicuous alterations by which it is possible to identify the condition. In the early stages the lymphadenoid hyperplasia is the most striking feature; later endothelial proliferation becomes marked and a notable increase in the fibrous tissue of the reticulum develops. In addition to the conspicuous increase in the lymphoid elements, giant cells, which may be mononuclear or polynuclear, appear in varying numbers. Reed is of the opinion that these elements are derived from the endothelial cells of the reticulum. Frequently, but not invariably, polymorphous eosinophile cells are abundant throughout the growth. In a case which I recently examined no eosinophiles were present in nodes removed a few weeks before death, but the specimens obtained at autopsy contained large numbers of these cells. The eosinophiles of the marrow and the myelocytes may be increased. The histology of the enlarged spleen and of the secondary growths in the liver and elsewhere is essentially similar to that of the involved nodes.

Tumors of Lymph-nodes.—If we except the foregoing enlargements from the tumors of lymph-nodes, the only important primary tumor of these structures is *sarcoma;* the alveolar, round-cell, melanotic, and mixed-cell forms occur in the order given. Sarcoma may be secondary as well as primary, but is less commonly so. The frequent secondary tumor of lymph-nodes is cancer. In all its forms *carcinoma* involves the lymph-spaces; the extent of this involvement of the primitive lymph paths, and the portability of the invading cells, together with the resistance of the individual, determine the rapidity with which the tumor cells reach the lymph-node anatomically nearest to the primary growth. Thus, the rapidly growing, almost spheric, cells of the encephaloid spread more rapidly than the squamous or flat irregular cell of the epithelioma. (See Tumors, pp. 312 and 323.) When cancer involves lymph-nodes, the histology of the primary tumor is usually as fully reproduced as the gland and its surrounding structure will admit.

Osteomata, chondromata, and endothelioma occasionally involve lymph-nodes, but are rare. Lymphangiomatous cysts sometimes occur in the lymph-nodes.

CHAPTER IV.

THYMUS BODY.[1]

In the last months of intrauterine life and during the first two years of infancy the thymus body may be justly called a gland, as it contains epithelial elements arranged in lobes, with subdivision into lobules, and a minute structure resembling that of certain glands. Even before birth displacement of the epithelial structures by lymphoid tissues is marked, and this substitution persists to the second, third, or fourth year. After this time atrophy progresses, and by the tenth year the adenoid structure has been replaced by fat and fibrous tissue, and at puberty, or shortly afterward, the gland can rarely be identified, or at most but a small vestige may be found.

Malposition and Malformation.—The organ may be absent, and there may be no evidence of its ever having developed. In other instances even in infancy it may be scarcely demonstrable. Accessory lobes, and even fully formed accessory glands, are occasionally observed. Rarely, the gland may be out of place, approaching the thyroid, or, less commonly, anterior to the heart and below its normal position; in some instances a lateral displacement may be present, and still less frequently the thymus vestige may be found in the peribronchial connective tissues. *Persistence of the gland*, either with or without enlargement, is occasionally observed. In the absence of any distinct overgrowth it may be questioned whether any symptoms or lesions result.

Atrophy of the thymus, as previously stated, is a normal process. Dudgeon divides the atrophies into primary and secondary; in the former the gland may weigh less than a gram, the lymphoid tissue is wasted, polynuclear giant cells are usually present, and many of Hassall's corpuscles are calcified. Hemorrhages are sometimes present and fatty infiltration is often conspicuous. Rührah makes this change the anatomic basis of marasmus. Secondary atrophy of the gland is seen in wasting diseases of all kinds, particularly tuberculosis. In the secondary atrophy, fibrosis is the most conspicuous change. Hyperplasia of the fibrous tissue, with increase in the lymphoid structure, giving rise to considerable glandular enlargement, sometimes called **thymic hypertrophy,** is occasionally seen. Normally, the thymus gland varies in weight between 5 and 10 gm. at the stage of its fullest development. The enlarged thymus may weigh from 20 to 100 gm., and may retain a weight of from 20 to 25 gm. in the adult. Very often this persistence or enlargement of the thymus is present without any

[1] The literature concerning the thymus gland is quite voluminous. For recent studies of the physiology of the organ see Paton and Goodall, "Jour. of Physiology," 1904, vol. xxxi, No. 1. Cecca and Zappi, "Bulle. del Sci. Med.," March, 1904. Paton, "Jour. of Physiol.," Dec. 30, 1904. Sinnhuber, "Zeit. f. klin. Med.," 1905, vol. 54, Nos. 1 and 2. For recent studies on the pathology of the gland consult Dudgeon, "Jour. of Path. and Bact.," 1904–1905, vol. x, p. 473; bibliography.

associated phenomena. In other instances it is observed in connection with goiter and with the lymphoid and adenoid enlargements of leukemia and Hodgkin's disease. Hérard, Bontemps, Grawitz, Marfan, Brouardel, and others believe that enlargement of the thymus is influential in the production of sudden death, particularly in children—so-called **thymic death.** Following thymic death, as well as asphyxia from other causes, *ecchymosis* and marked congestion are commonly found in the thymus. *Petechiæ* and *ecchymoses*, or even larger *hemorrhagic infiltrations*, are also occasionally observed in the gland in scurvy and in acute infections occurring during infancy.

Lymphatism, status lymphaticus, and **lymphatic constitution** are names applied to a condition in which there is general hyperplasia of many lymphoid tissues, including the thymus gland. The spleen is usually enlarged, Peyer's patches are prominent, and sudden death is not uncommon. These patients bear anesthesia badly, and sudden death has occurred during minor operations under local anesthetics. The condition may be associated with rickets. Ohlmacher has noted the coincidence of status lymphaticus and epilepsy. Sudden death in these cases has been attributed to pressure on the trachea, heart, or great vessels, and to the action of toxic substances present in the blood.

Little is known of inflammations, degenerations, and necroses that occur in the thymus. That the body is subject to embolism is indicated by the occurrence of abscesses in pyemia, and sometimes in septicemia.

In common with other tissues it is liable to invasion by miliary tubercles, and occasionally contains the caseous, fibrocaseous, or cretaceous nodules of chronic tuberculous infection. Gummata of the thymus have been observed.

Primary tumors of the thymus gland are rare. By reason of the presence of epithelium, *carcinoma* is probably the most frequent tumor; however, *sarcoma* of the round-cell type is relatively frequent. Lymphoid proliferation occurs in Hodgkin's disease and in leukemia.

CHAPTER V.

SEROUS MEMBRANES.

The **normal serous membrane** is composed of a flattened layer of connective-tissue cells (endothelium) resting upon a subserous network of loose connective tissue in which ramify the blood-vessels, lymphatics, and nerves. The membrane is lubricated by a serous fluid, about the origin of which there has been considerable discussion. The older view, that it is a transudate, must be modified. The statement that the fluid normally present in the serous cavities is a transudate rather than a secretion is based upon the view that lymph is not a secretion; this matter has been already discussed, and need not be reviewed; the reader is referred to the article on Edema, page 267. An important histologic and physiologic fact, of great practical significance, is the demonstration that the serous cavity is in direct communication with the lymph-spaces of the subserosa and, in some instances, with the lymph-paths of the organs and structures covered. The exact character of this communication is still a subject of controversy; the older view that the lymphatics adjacent to the serous membranes communicated with the cavity by open-mouthed vessels (stomata) has been attacked and somewhat modified, but the communication has not been disproved. If India ink be injected into the subserosa, the granules appear in the serous cavities; and if this substance, or other material containing finely divided particles, be injected into the peritoneum, the granules may be traced in the diaphragm and are sometimes found in the lymph-nodes that drain the area. The importance of this demonstration can not be overestimated, as it explains the occurrence of inflammation of the serous membranes covering affected viscera, makes it evident why pleurisy frequently accompanies pneumonia (epipneumonic pleurisy), why inflammation of the pleura may precede or follow inflammation of the peritoneum, and also renders it possible to understand the changes occurring in the viscera as a result of infection of the overlying serosa. The blood-vessels supplying nourishment to the serous membrane constitute a fine capillary network distributed in the subserosa; the thin endothelial investment readily permits the absorption of toxic substances from a serous cavity and offers little resistance to the passage of infectious material from the underlying capillaries to the serous surface.

The serous cavities of the body are the *peritoneum*, the *pleuræ*, the *pericardium*, the *serous covering of the brain and cord*, the *synovial structures of the joints and tendon-sheaths*, and the lining membranes of the *bursæ*. When one of these membranes is examined in its normal condition, the surface is found to be moist, smooth and shining, and the membrane thin and transparent. The color is uniform with that of the tissue which it covers, and where two layers of the serous membrane have nothing between them but the fibrous or fibro-elastic network on

which they rest, it may be practically true that the membrane is colorless. The normal serum of the cavity is a clear fluid, usually of a light straw-color; it may, however, be stained by osmosed coloring-matter, as the coloring-matter of the blood, which may pass through the heart postmortem and tinge the pericardial fluid.

The quantity of fluid present in any given serous membrane is dependent upon the amount in the connective tissues elsewhere, as well as the surface area of the membrane in question, and must, therefore, vary in quantity. If the patient has died slowly, and a general lymph stasis has ensued from the gradual slowing of the circulation, more fluid will be found in the serous sacs than under conditions of rapid death. The amount of fluid that can be collected will approximate, in the peritoneum, from 8 to 50 c.c.; in the pleura, from 30 to 100 c.c.; in the pericardium, from 4 to 30 c c.

If during life, for any reason, there is slowing of the circulation leaving a serous membrane or the organ which it incloses, there is a disposition for fluid to accumulate in the serous cavity, just as obstruction to the onward flow of blood in any part of the body leads to the infiltration of the lymph-spaces with serum. Such an accumulation constitutes what is often spoken of as **dropsy of a serous cavity.** *Ascites*, or *hydroperitoneum*, from obstructive lesions in the liver is an example of this condition. The accumulation of fluid in the pleura (*hydrothorax*) in pulmonary edema and general dropsy is a second instance; similar conditions may cause *hydropericardium*. Steele[1] and also Stengel have shown that in the hydrothorax of heart disease the effusion is sometimes unilateral, in which case it is commonly restricted to the right side, and when bilateral the larger quantity of fluid is usually in the right pleura. It is thought that this difference in the two sides may depend upon pressure of the enlarged right heart on the root of the right lung and the vena azygos major; it is also to be remembered that the serous surface of the right pleura is the larger, and that any condition tending to increase the output of fluid from the serosa would be likely to give rise to a larger quantity upon the right side. With enlargement of the left heart there is usually a tendency toward a left-sided effusion or at least a larger quantity of fluid in the left pleura. The accumulated fluids interfere mechanically with the function of the organs in the affected cavity, and increase the venous congestion, which may have been the original cause.

Accumulations of serum, without any gross evidence of inflammation, occasionally occur in serous cavities where the membrane is infiltrated by miliary tubercles. The tubercles surrounding and obstructing the small vessels—arteriole, capillary, and vein—lead to extravasation exactly as would any other obstructive lesion; it is also probable that the irritation produced by the tubercle bacillus or its poisons increases the permeability of the endothelium or induces an inflammation of such a low order that the resulting fluid possesses more of the characters of a transudate than of an exudate. The process is most frequent in the peritoneum, where not uncommonly gallons of fluid may be, at different times, drawn off, only to reaccumulate, as in the ascites due to obstruction of the portal vein radicles in the liver.

In addition to the dropsical conditions arising from chronic diseases

[1] "Jour. Amer. Med. Assoc.," Oct. 1, 1904; bibliography.

of the heart and of the kidneys, and the local obstruction to the circulation secondary to cirrhosis or protracted congestion of the liver, chronic or persistent irritation of any kind affecting a serous membrane is likely to induce more or less serous accumulation within its cavity. Such persistent irritation is occasionally observed in the joints, giving rise to *hydrops arthrosis*, sometimes called joint dropsy.

The fluid present in dropsical conditions of serous membranes differs materially in composition from the inflammatory exudates. Its specific gravity is usually low—1015 or lower. As a rule, it is clear; occasionally, however, it may be cloudy. Cloudiness is more frequent in hydroperitoneum than in dropsies of other serous cavities. When the accumulation is due to obstruction of the lacteals, as it may be in the peritoneum, the milky opacity is to be attributed to the presence of fat globules. These are usually easily recognized under the microscope, and may be further identified by the usual tests for fat. (See p. 244.) It has been the custom to assume that the abundant presence of leukocytes arose only in connection with inflammation, but Poljakoff[1] has reported a case in which the milkiness of the transudate was apparently due entirely to the presence of white blood-cells. In Poljakoff's case the low specific gravity (1009) favored the exclusion of inflammation. In true milky ascites the fluid, on standing, usually evinces partial separation into three layers: the uppermost layer is milky or cream-like, and contains fat; the sediment is composed of leukocytes and cellular detritus, while the intervening layer may be quite clear. True **chylous ascites**[2] results from the escape of chyle into the peritoneal cavity and may be due to obstruction of the thoracic duct, disease of the receptaculum or lacteals, and to the rupture of chylous vessels or cysts in the mesentery. In the thorax the condition results from injuries and rarely from neoplastic or tuberculous invasion of the thoracic duct. True chylous fluids contain sugar, and the melting-point of the fat approximates that of the fats ingested. The accumulations are usually rapid and, after removal, quickly reform. Those fluids in which the resemblance to chylous liquids is striking, but in which the opacity is not due to fat derived from the chyle, are called chyliform. **Chyliform ascites** is the commonest of these accumulations. Chyliform fluids accumulate slowly, are usually relatively rich in cells, are not infrequently associated with neoplastic involvement of the serosa, commonly contain no sugar, and the fat content is not influenced by the quantity or character of the ingested fats. Chemic examination shows that the amount of fat is small, rarely attaining 0.15 per cent. In true chylous ascites the quantity of fat varies between one and three per cent., and sometimes is much more. Pagenstecher believes that chyliform fluids are produced by degenerative changes in the contained cells resulting in the production of molecular fat; such transformation may explain some cases, but it is probable that in most instances the cloudiness is due to a proteid resembling that which causes the opacity of fat-free milk.

The order in which the serous cavities of the body are examined is: (1) Peritoneum; (2) pleura; (3) pericardium; and (4) the serous membranes covering the brain and cord. The processes in each of these,

[1] "Berliner klin. Woch.," 1900, No. 1, p. 9.

[2] The subject of chylous and chyliform ascites is fully reviewed by Boston, "Jour. Amer. Med. Assoc.," Feb. 18, 1905, p. 513; bibliography.

when affected by disease, vary so little—the variation depending not so much upon the membrane as upon the surrounding structures—that it is possible to study in detail disease affecting one of the cavities and apply the knowledge thus acquired to any or all of the other serous membranes with but slight modification: *e. g.*, the brain, being inclosed in a rigid covering (the skull), is never surrounded by large accumulations of fluid so constantly found in inflammations of the pleura.

Malpositions of the various serous membranes are determined by ectopia of the viscera contained in the cavity, and, in the absence of such conditions, are rarely observed. Malposition of the heart leads to displacements of the pericardium; in hernias or other malpositions of the abdominal viscera or lungs the serosa accompanies the ectopic viscus. The same general statement applies to malformation of other serous membranes; the surface distribution of the serosæ is determined by the contour of the enclosed organs and the shape of the parietes which the serous membrane lines; when these structures are normal, developmental defect in the enveloping serosa is exceedingly rare.

Malformation of the pericardium occurs but rarely, and usually consists of *partial* or *complete absence* of the membrane. One should not be misled by considering universally adherent pericardium as illustrative of absence of the organ. Normally, the phrenic nerves are widely separated by the pericardium, but in those cases of absence of the pericardium that have been reported the two nerves are almost side by side. This will, therefore, aid in demonstrating that the pericardium was present at one time, and that inflammation sealed its walls together. Evidences of past inflammation are usually to be found. Adhesions to the surrounding structures, thickening of the adjacent pleura, and sometimes induration of the mediastinal tissues will offer further aid in recognizing the essential character of the process. Sometimes adventitial folds and duplications may be found near the base of the heart, great vessels, or along the margins of the auricles. Rohn[1] records four instances in each of which a pericardial diverticulum was present; usually such a sac or pouch projects into the mediastinal tissues and toward the right side. Occasionally fenestra between the pleura or peritoneum, and pericardial cavity, are observed.

Maculæ albidæ, *tendinous patches*, or *white* or *milk spots* on the pericardium, are occasionally found, and are usually due to the heart thumping, at each pulsation, against some hard body, such as a prominent costal cartilage, or, more rarely, the vertebræ. These spots are to be differentiated from the deeper lesions of fibroid change in the cardiac muscle by the former being thin, superficial, and not in the muscle, but on its surface. It is generally admitted that the so-called milk spots do not have their origin in any acute inflammatory condition. Each spot is essentially a localized fibrosis, commonly restricted to the pericardium and subpericardial tissue, and rarely involving the myocardium. When the fibrosis extends into the muscle, it is usually only a very superficial invasion, although, in rare cases, local extension of the newly formed fibrous tissue into the cardiac wall may be observed. In such instances it is quite impossible to say that the condition did not first involve the muscle—an interstitial myocardial fibrosis. The spots are pure white, grayish-white, or even pearly in color; rarely, of a pinkish

[1] "Wien. klin. Woch.," 1903, No. 18.

hue. Occasionally, a spot may be slightly calcareous. They are usually situated in the visceral pericardium near the base or anterior surface of the right ventricle or near the apex of the left. Milk spots are infrequent in childhood, and are more often present with advancing years. They are more frequent in males than in females. Enlarged hearts are more commonly affected; particularly is this the case in hypertrophy. Structures possessing the same general characters and histology are sometimes found on other viscera. The spleen is often affected, and the liver less frequently. The condition is a local fibrous hyperplasia due to repeated slight injuries or other form of circumscribed irritation.

Infiltrations.—Pigment is rarely found in the pericardium. Fatty infiltration is occasionally observed. Calcareous areas may be seen, particularly if the membrane has ever been the seat of inflammation. Ernst Jones[1] collected 58 cases of calcified pericardium. The condition is twice as common in the male as in the female. In most of the cases there were no clinical signs indicative of the condition. The process is essentially chronic, persisting for fifteen or twenty years. In thirteen per cent. of the collected cases there was a probability that the condition was secondary to suppurative pericarditis. Sometimes in fibrous areas resulting from past pericardial inflammation extensive calcareous infiltration is found. At times this calcific deposit may be so great that one can but wonder how the heart has maintained its contractile power; the whole of the pericardium may show more or less calcareous infiltration, and at points the calcific layer may be five millimeters in thickness. Such extensive calcareous infiltration is usually to be regarded as evidence of past inflammation, and it is doubtful whether calcification occurs in a serous membrane that has not been the seat of some inflammatory lesion.

Degenerations.—Fatty, myxomatous, hyaline, and granular changes occur, but not frequently.

Inflammation of the pericardium (**pericarditis**) is analogous to inflammation of the peritoneum (**peritonitis**), inflammation of the pleura (**pleuritis,** or pleurisy), inflammation of the meninges (**meningitis**), inflammation of the synovial membranes (**synovitis**), inflammation of the bursæ (**bursitis**), inflammation of the tendon-sheaths (**thecitis**). The term **serositis** is used to include any serous membrane inflammation. When a number of serosæ are simultaneously or sequentially affected the names **polyserositis, multiple serositis,** and **polyorrhomenitis** may be employed.

Inflammations of the serous membranes may be *primary* or *secondary*. The primary inflammations are sometimes called idiopathic, based upon the impossibility of definitely ascertaining the essential etiologic factor. Nearly all the inflammatory conditions affecting the serous membranes are secondary in point of origin, and therefore are practically always associated with some other morbid process. One of the most frequent causes of inflammation of the serous surfaces is extension of an inflammatory process from adjacent structures. Of the many examples that might be given for this condition, the following should be mentioned: Meningitis secondary to disease of the ethmoid, sphenoid, and mastoid sinuses, and from diseases of the middle ear or cranial bones; pericarditis secondary to pleurisy or mediastinitis, ulcer-

[1] "Path. Soc. of London," May 21, 1901.

ative lesions in the esophagus or stomach, and pericardial inflammation due to infectious processes involving the myocardium; pleurisy secondary to diseases of the underlying pulmonary tissue; peritonitis resulting from perforation of the intestine as well as from suppurative, perforative, or gangrenous processes in the appendix or intestine; and extension of infection from the pelvic viscera, particularly in the female. The circuitous route usually taken by suppurative and ulcerative processes occurring in organs adjacent to the diaphragm may lead to unusual, or even extraordinary, combinations of pathologic conditions. Thus, hepatic abscess may induce peritonitis or pleurisy, or both, depending upon whether its extension is directed toward the diaphragm, through which it may perforate, extending even into the lung and discharging its contents through a bronchus. Gastric ulcer and carcinoma of the stomach may perforate the peritoneum, pleura, or pericardium.

Inflammations of the serous membranes may also arise as a result of specific agents circulating in the blood. In pyemia and septicemia inflammations involving the joints, pericardium, pleura, meninges, and peritoneum are not uncommon. Inflammations of serous membranes are sometimes said to be *chemic* or *aseptic*, in contradistinction to inflammatory conditions arising from demonstrable infection. Thus, it has been held that the inflammation of the joints and of the pericardium in rheumatism, for example, was due to the presence in the circulating blood of irritants probably the result of faulty metabolism. About fifty per cent. of the cases of pericarditis are of rheumatic origin. The trend of opinion at present seems to be toward the belief that rheumatism is a bacterial disease (see Diplococcus rheumaticus, p. 112), and if such origin can be satisfactorily demonstrated, its time-honored use as an example of a nonbacterial cause of inflammation of serous membranes can not be justified, and the possibility of distinctly chemic or aseptic serous inflammation must appear less admissible.

Trauma must be admitted as a cause of inflammation of the serous membranes; meningitis may follow cranial or spinal injuries; pleurisy or pericarditis[1] may be produced by penetrating wounds, contusions, and crushes of the thoracic wall; peritonitis may follow abdominal trauma, and synovitis and bursitis are frequently of traumatic origin. That the inflammation is the direct consequence of the injury seems in most cases to be doubtful; the frequency with which surgeons attack the serous membranes clearly shows that, in the absence of infection, these structures tolerate considerable violence. Schachner[2] has collected 150 recorded instances in which foreign bodies have been accidentally left in the abdominal cavity; if aseptic, and nonirritating, encapsulation and enclosure by adhesions result. The danger from trauma is largely due to the fact that the injured membrane is frequently infected, or its resistance to infection so lowered that it may readily be attacked by bacreria. Injuries that destroy tissue or permit blood to accumulate in the terous cavities invite infection; therein lies the greatest danger. The separative effort necessary for healing aseptic wounds of the serosæ scarcely rises to the dignity of an inflammation; at most, it produces nothing more than a slight plastic exudate terminating in the formation of fibrous tissue.

[1] Pleasants, "Bull. of Johns Hopkins Hospital," 1903, vol. xiv, p. 124.
[2] "Annals of Surgery," November, 1901.

Aneurysm of the heart or of the aorta—the latter presenting in the pericardial cavity—may be attended by pericarditis. Allbutt[1] recognizes a dry plastic pericarditis due to aortitis and usually involving the pericardium contiguous to the affected aorta. Malignant growths and chronic infectious processes attacking the serous membranes usually induce inflammation. Embolism involving the viscera covered by serosa may, if the infarct reach the surface of the organ, give rise to a serositis, the character of which must depend upon the nature of the embolic process. Miller[2] holds that many cases of postoperative pleurisy are of embolic origin.

Inflammation of the serous membranes may occur in the course of many infectious diseases. In a number of these it is due to the specific organism of the affection which it complicates. Thus, in croupous pneumonia, pleurisy is practically always present, the pericardium frequently affected, and peritonitis, meningitis, and synovitis sometimes result from the pneumococcemia. Keen[3] collected 9 cases of pleurisy, 2 cases of pericarditis, 15 of meningitis, and 98 of arthritis complicating typhoid fever. In many of these cases the typhoid bacillus was obtained, sometimes in pure culture. Other cases of serous membrane inflammation, due to the typhoid bacillus, have been reported by Widal and Lemierre,[4] Kichel,[5] Gourand,[6] Gordinier,[7] Cole[8] and others. Sears[9] states that Betke observed 58 cases of pleurisy in 1420 instances of typhoid. In influenza, pleurisy is sometimes observed, peritonitis has been known to occur, joint complications are not altogether rare, and meningitis due to the Bacillus influenzæ is occasionally seen; according to Mya,[10] there are 17 recorded instances of grippal cerebrospinal meningitis. The serositis sometimes complicating erysipelas is due to the hematogenous dissemination of the streptococcus. In a number of infectious diseases serous membrane inflammations due to associated or intercurrent infections are sometimes observed. With this group of cases should be included the inflammations of the serosæ occurring in scarlet fever, smallpox, measles, and allied acute infectious diseases, concerning the specific cause of which additional information is needed.

In the chronic forms of nephritis, particularly in contracted kidney, pericarditis and, although less commonly, pleurisy are not infrequent. These affections are also seen in gout and diabetes. At one time it was maintained that, in the diseases mentioned, toxic substances circulating in the blood were responsible for the complicating inflammation; it is now generally held that the serositis is bacterial in origin and that the diseases with which it occurs favor the action of microorganisms by lessening tissue resistance and facilitating the dissemination and colonization of germs which enter the circulation. In many of these cases the complication is a terminal infection.

[1] "Lancet," July 18, 1903, p. 143.
[2] "Amer. Med.," Aug. 2, 1902.
[3] "Surgical Complications and Sequels of Typhoid Fever," 1898.
[4] "C. R. Soc. de Biol.," 1903, vol. lv, p. 1431.
[5] "Gaz. des Hôp.," August 30, 1901.
[6] "Gaz. des Hôp.," 1903, lxxvi, p. 375.
[7] "Amer. Jour. of Med. Sci.," Jan., 1901.
[8] "Johns Hopkins Hospital Bull.," Feb., 1904, p. 62.
[9] "Med. and Surg. Reports of Boston City Hospital," 1902, 13th series, p. 22
[10] "Gazz. Osped.," March 1, 1903.

Bacteriology of Serositis.—Reference has already been made to the serous membrane inflammations accompanying typhoid, pneumonia, influenza, erysipelas, and other infectious diseases in which the organism, entering the circulation, localizes in one or more serosæ. There are a number of bacteria which often produce serous membrane inflammation without evident antecedent infection of other structures. The pneumococcus is frequently found in serositis. According to Parker,[1] seventy-five per cent. of the cases of empyema in children are pneumococcal; exactly what proportion of these are metapneumonic—follow pneumonia—it is difficult to say. Often it is impossible to determine, with any degree of accuracy, by what route the infection occurred. When the pleura is involved, it is reasonable to assume that the organism entered through the lungs; in primary pneumococcal meningitis the infection probably traversed the facial or cranial air sinuses. It seems likely that pneumococcal pericarditis is always the result of hematogenous infection. According to Jensen, pneumococcal peritonitis results from infection through a wound, through the diaphragm, through the intestine or genital tract, by the blood, or from pneumococcic foci in an abdominal organ. Ghön states that pneumococcic peritonitis[2] frequently complicates cancer of the stomach. The pneumococcic forms of arthritis are hematogenous in origin and are rarely primary. The serosæ particularly prone to infection by the gonococcus are the synovial membranes and peritoneum. Hunner and Harris were able to collect 39 cases of gonococcal peritonitis.[3] Gonorrheal rheumatism is essentially a synovitis, although other joint structures may be affected. The pyogenic cocci and the Streptococcus pyogenes are frequently found in suppurative inflammations of the serous membranes. McCollom and Blake[4] report two instances of streptococcal peritonitis in 8000 cases of scarlet fever. In 270 cases of peritonitis, Dudgeon and Sargent[5] found the Staphylococcus pyogenes albus in 108. Manahan[6] found streptococci alone or associated with other bacteria in about fifty per cent. of the cases coming to autopsy. In perforative lesions involving the intestine or appendix the colon bacillus is practically always present and, like the typhoid bacillus, may give rise to peritonitis without demonstrable lesion in the continuity of the intestinal wall (propagative infection). The bacillus coli is not infrequently present in inflammations of serous membranes other than the peritoneum. The meningococcus[7] is the usual cause of epidemic cerebrospinal meningitis and has also been observed in pericarditis and pleurisy.

[1] "Brit. Med. Jour.," May 9, 1903, p. 1081.

[2] "Wien. klin. Woch.," March 10, 1904, p. 267. Mathews, "Annals of Surgery," Nov., 1904, p. 698. de Quervain, "Corresp. Blatt. f. Schweizer Aertze," vol. xxxii, No. 15.

[3] Dowd, "Annals of Surgery," Feb., 1902. Hunner and Harris, "Bull. of Johns Hopkins Hospital," June, 1902, vol. xiii, p. 135. Putman, "The Post-graduate," Oct., 1902, p. 1117. Krause, "Berl. klin. Woch.," May 9, 1904. Huber, "Arch. of Pediatrics," Dec., 1904. Galvagne, "Annales des Maladies des Organes Genito-Urinaires," 1904, No. 13, p. 1039. Wynn, "Lancet," Feb. 11, 1905, p. 352. See also Gonococcus, p. 107.

[4] "Boston Med. and Surg. Jour.," Dec. 10, 1903.

[5] "Lancet," Feb. 25, 1905, p. 474.

[6] "Boston Med. and Surg. Jour.," March 23, 1905, p. 346.

[7] See page 111; also Cerebrospinal Meningitis.

The tubercle bacillus[1] occupies an all-important relation to the production of serous membrane inflammations; all serosæ are susceptible to its action, but the pleuræ, pericardium, meninges, and peritoneum are more frequently involved than the synovial membranes, tendon-sheaths, or bursæ. There is little reason for believing that the serositis produced by the tubercle bacillus is ever primary, although cases occur in which it is difficult, if not impossible, to demonstrate the initial infection from which the bacillus reached the serous membrane. The frequency of pleurisy due to the tubercle bacillus is variously estimated at from fifty-five per cent. to ninety-four per cent. of all cases observed; the studies of Eichhorst indicate that sixty per cent. to sixty-five per cent. of those with serous effusion contain fluid capable of producing tuberculosis in inoculated animals.

Among the bacteria occasionally found in serositis may be mentioned the bacillus of Friedländer, Bacillus pyocyaneus, Bacillus pyogenes fœtidus, Bacillus aerogenes capsulatus, and, although less commonly, other anaerobic bacteria.[2] In exceptional cases the condition is produced by members of the actinomyces group.[3] Schwartz[4] reports a case of appendicitis and encysted peritonitis due to a yeast.

Classification of serous membrane inflammations may be based on the etiology, extent, and duration, or the clinical and anatomic characters. Those inflammations not due to bacteria or their toxins were called simple, and distinguished from the infective by the absence of micro-organisms. Extended knowledge indicates that serositis, in practically all its forms, is infective in origin, and the more recent tendency is to give up the names simple pleurisy, simple pericarditis, etc. *Idiopathic* or *cryptogenic inflammations* include those in which the source of the infection can not be determined. Inflammations in which the infection was introduced from without, as by operation and other wounds, are called *exogenous*. Those resulting from invasion of a serosa by infectious processes originating in some adjacent structure are known as *endogenous*, and include the so-called secondary form of serous membrane inflammation.

In certain cases names are utilized to indicate the extent of the inflammatory process; in *localized* or *circumscribed serositis*, a part only of the affected serous membrane is involved; in the *general* or *diffuse* form the entire serosa is inflamed. *Parietal* and *visceral* forms have been described. Some of the localized types of serous membrane inflammation have received special names indicating the particular part of the serosa affected. As examples of this method of classification may be mentioned pelvic peritonitis, diaphragmatic pleurisy, interlobar pleurisy, apical pleurisy, and basilar meningitis.

The terms *acute* and *chronic*, as applied to serous membrane inflammation, usually imply something more than mere duration, and constitute

[1] Cornet, "Tuberculosis, Acute General Miliary Tuberculosis," Nothnagel's Encyclopedia, American edition, 1904, p. 189. Grober, "Centralbl. f. inn. Med.," 1902, No. 10. Murray, "Lancet," 1902. Bonney, "Med. News," Feb. 18, 1905, p. 289.

[2] Ghön and Sacs, "Centralbl. f. Bakt.," Jan. 25, 1905, p. 1, and Feb. 18, 1905, p. 131.

[3] MacCallum, "Centralbl. f. Bakt.," May 14, 1902, also Mathews, "Practitioner," Feb., 1905, p. 197.

[4] "Revue de Chir.," July, 1903, p. 122.

a basis upon which anatomic classification rests. The study of the morbid anatomy of serous membrane inflammations renders it possible to divide the acute into (1) serous, (2) serofibrinous, (3) fibrinous or plastic, and (4) suppurative. Some of the chronic inflammations of the serous membrane may be little more than the consequences of the acute forms. It is possible, however, to recognize certain subdivisions and more or less distinct types. Nicholls[1] suggests dividing the chronic inflammations into (1) exudative, (2) exudative and adhesive, and (3) chronic hyperplastic; the latter is also called progressive hyaloserositis.

Morbid Anatomy of Acute Serositis.—In this form it is usually possible to recognize definite stages which often blend so that distinct separation of one from another may be quite impossible. In some cases the inflammation seems to linger in one stage or the phenomena may be restricted to those that are ordinarily observed in this particular period in the evolution of a serositis. In the first stage the membrane is dry, red and injected, slightly opaque and perceptibly roughened. It may be sticky, and it always presents, over the inflamed area, a dull or velvety surface, in contrast to the shining luster of the normal. Histologically, at this stage the subserous capillaries are distended with blood. The areas of capillary hyperemia are scattered over the membrane irregularly, and appear as though smears of carmin stain had been daubed, here and there, over the affected membrane; the diffuse character of the discoloration has been likened to a blush; rarely, if ever, is the hyperemic capillary distention universal. The *morbid physiology* is shown in the friction sounds discernible on auscultation, and the fremitus, both of which are due to the friction of roughened and dry surfaces rubbing against each other. The pain of this stage is probably the result of mechanical injury to the nerve filaments, and chiefly to the irritation of the nerves by bacterial toxins and the chemic bodies engendered by the changes in cell metabolism. It seems probable that the fever is due to the same bodies entering the circulation.

The second stage corresponds to the formation of the exudate, and might, with propriety, be called the stage of exudation. The liquor sanguinis escapes from the distended capillaries, and, upon reaching the surface of the membrane, splits into fibrin and serum, the former coating the surface of the serosa, the latter finding room in the cavity. With the escape of the plasma the leukocytes migrate into the fibrinous and serous exudate It is also probable that the flattened connective-tissue cells are to some degree detached. Should the exudate be slight, and should the serum be rapidly absorbed, but little remaining in the cavity, clinically, the inflammation is spoken of as *plastic* or *fibrinous;* if, however, the effusion be rich in serum and poor in cells and fibrin, the process is called *serous.* In the *serofibrinous serositis* the exudate is usually large, and the fibrin and cells abundant. If the first stage be called the stage of engorgement or hyperemia, the appearance of the exudate initiates the stage of exudation.

In this stage the membrane is found either partly or completely covered with fibrin, the degree of cohesion being dependent upon the thickness of the layer and upon its age. The fluid in the serous sac differs

[1] "American Medicine," June 21, 1902, p. 1062; "Jour. Amer. Med. Assoc.," March 14, 1903, p. 696; and "Studies from the Royal Victoria Hospital, Montreal," April, 1902, vol. 1, No. 3.

from the normal serum in that it is opaque and contains fibrinous flocculi; the opacity is partly the result of the fibrin present, but is chiefly due to the large number of suspended leukocytes. The soft, downy mass of fibrin hanging in shreds has led to the heart at this stage being called the *cor villosum;* it is also known as the *cor hirsutum.* (See Fig. 232.) Laennec compared the appearance to that resulting from the separation of two smooth surfaces of wood between which had been pressed a pat of butter, and hence the term "bread-and-butter appearance." The thick, shaggy layer may remain adherent to the membrane, or the fibrin may be whipped off to a greater or lesser degree by the movements of the inclosed organ. The color varies. Commonly the inflammatory exudate is white or yellowish-white; sometimes, however, it is brown, yellowish-brown, or even brownish-red. These modifications in color are due to the dissolution of hemal elements in the exudate. In the earlier stages the exudate may be readily stripped from the serous surface, and may even show lamination, as though successive layers had been thrown out, the lowermost and overlying strata being pushed upward by the succeeding layer. The amount of serum present in the cavity determines whether inflammation should be called in this stage dry or moist. Where absorption has been rapid and the serum has thereby been removed as rapidly as formed, or nearly so, the serositis is said to be dry, plastic, or fibrinous.

The studies of Beattie[1] were directed toward determining the period at which the different elements appeared in the inflammatory exudate; working with various bacteria, including pyogenic staphylococci and tubercle bacilli, and also with foreign bodies, he found that during the first two hours, following the application of the irritant, the fluid was clear, resembling normal serum. In from one to two hours after the injection the polymorphonuclear cells began to appear in numbers, and by the third hour were greatly increased. In from four to eight hours migration of the mononuclear leukocytes began, and by the twelfth hour these cells were fairly abundant. Turbidity and viscosity of the fluid became progressively more intense, reaching the maximum about twenty-four to forty-eight hours after the introduction of the irritant. After this time the character of the fluid, in fatal cases, was different from that in animals which recovered. In nonfatal cases the fluid increased and was more abundant in fifty-four to seventy-two hours; during this time the exudate appeared watery, by the fourth day it was clear, and by the fifth normal. In these cases the polymorphonuclear cells, abundant during the first day and a half, became less conspicuous and disappeared between the sixtieth and seventieth hours. Beattie is of the opinion that the mononuclear cells are derived from the blood and also from the endothelium, particularly of the omentum. The polymorphonuclear leukocytes, lymphocytes, hyaline cells, endothelium, and plasma cells, all manifest varying degrees of phagocytic power.

The specific gravity of the fluid is usually higher than in the pure transudates and may be 1.040; commonly it varies between 1.015 and 1.025. As a result of destruction of the leukocytes, the xanthin bases are increased. Galdi and Appiani[2] have shown that the quantity of

[1] "Jour. of Path. and Bact.," vol. viii, June, 1902.
[2] "Rif. Med.," Dec. 14, 1904.

uric acid is proportionate to the specific gravity, the total amount of hydrogen, and quantity of proteids, all of which are increased. Urea, sugar, and peptone are usually present. Coriat[1] has demonstrated Bence-Jones albumin in the fluid from pleuritic effusion.

The amount of accumulated exudate in the pericardial cavity may be from 100 c.c. to 200 c.c.; occasionally as much as a liter, and rarely more. According to Aporti,[2] pericardial effusions amounting to less than 150 c.c. to 250 c.c. can not, with certainty, be clinically detected, and distensibility of the pericardium does not permit the rapid formation of an exudate exceeding 650 c.c. to 700 c.c. When the fluid accumulates more slowly, has been withdrawn and permitted to reform, or is purulent, the pericardial sac slowly yields and may readily contain larger amounts. When the quantity of fluid exceeds 200 c.c. or 300 c.c. the intrapericardial pressure becomes notably augmented. Glynn[3] found that in an accumulation of approximately 700 c.c., in a boy aged seventeen years, the pressure at the beginning of paracentesis pericardii was + 2.1 cm., and at the end of the operation fell to —2 cm. The quantity of fluid in the pleura is influenced by the presence of adhesions, the character and duration of the inflammation, and commonly is larger on the right than on the left side. Of the 200 cases studied by Delafield,[4] the quantity was between 3000 c.c. and 3500 c.c. in 6; between 2000 c.c. and 2500 c.c. in 23; 1500 c.c. to 2000 c.c. in 37; 1000 c.c. to 1500 c.c. in 55; 500 c.c. to 1000 c.c. in 49; and in 30 cases there was between 100 c.c. and 400 c.c. The quantity of fluid may far exceed the maximum observed in Delafield's cases. The changes in pressure result in the lung being displaced backward, upward, and inward toward the hilum of the organ, the mediastinal tissues are forced toward the unaffected side, and the diaphragm descends. During the earlier stages of the process spasticity of the intercostal muscles narrows the space between the ribs, and later degenerative and necrotic changes affecting these structures[5] may be followed by relaxation and intercostal bulging. Rohrer[6] was the first to demonstrate structural changes in the diaphragm resulting from inflammation of either one of the three contiguous serosæ; I have been able to verify his observations.[7] In many cases of pleurisy the lymphatics of the pulmonary tissue contain leukocytes and fibrin, and similar bodies have been found in the lymph-nodes of the hilum of the lung. In inflammation of the peritoneum the analogous abdominal structures show essentially the same changes. In both locations the alteration is produced by irritants traversing the lymphatics draining the affected area. In this way the *lymphogenous interstitial pneumonia*, which may be suppurative or, in the more chronic cases, fibroid, is produced. In the heart the myocardium, contiguous to the inflamed serosa, is frequently degenerated and may be infiltrated by the inflammatory products (*peri-*

[1] "Amer. Jour. of Med. Sci.," Oct., 1903, p. 631.
[2] "Centralbl. f. inn. Med.," July 14, 1900.
[3] "Jour. Amer. Med. Assoc.," June 1, 1901.
[4] "Amer. Jour. of Med. Sci.," Dec., 1902, p. 939.
[5] Coplin, "Amer. Jour. of Med. Sci.," May, 1904; "Proceed. of the Path. Soc. of Phila.," Jan. 28, 1904.
[6] "Maryland Med. Jour.," Sept., 1902, p. 391.
[7] For illustration showing coagulation necrosis in intercostal muscles see Fig. 143, p. 251.

cardiomyocarditis). In meningitis[1] the contiguous nervous tissue is the seat of manifest degenerative changes and the nerve-trunks of the affected area are infiltrated. Laignel-Lavastine[2] has shown that in peritonitis the solar plexus is affected; in the acute manifestations the lesions are essentially parenchymatous; in the chronic cases the interstitial changes are more conspicuous.

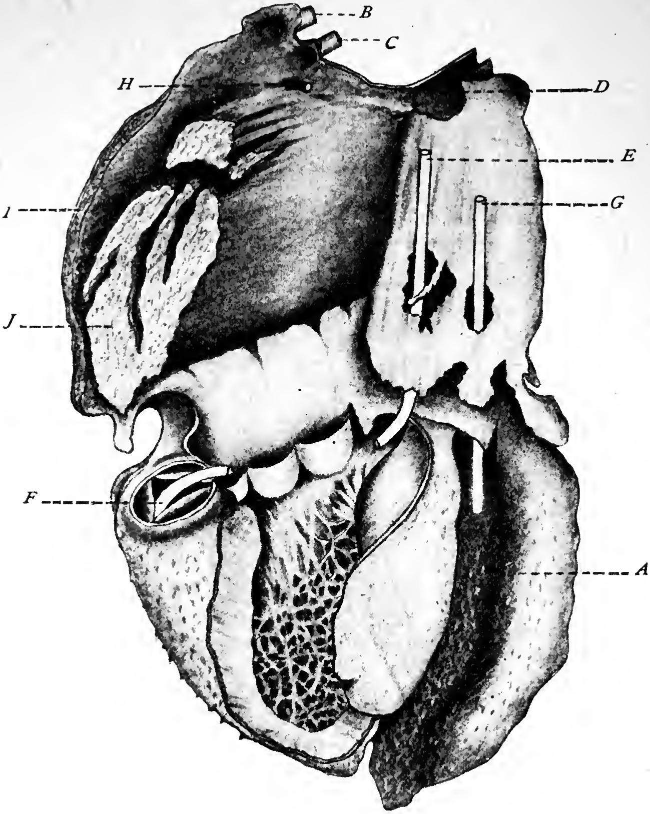


FIG. 232.—HEART SHOWING VILLOUS PERICARDITIS; ASCENDING AND TRANSVERSE PORTION OF ARCH OF AORTA SHOWING ANEURYSM WITH CONTAINED CLOT, AND RUPTURES INTO PULMONARY ARTERY AND PERICARDIUM.

A. Part of the parietal pericardium, showing the fibrinous deposit and minute villi. A similar appearance is present on the visceral pericardium. *B*. Innominate artery. *C*. Left common carotid. *D*. Left subclavian. *E*. Catheter passing through the clot in the aneurysm of the aorta and into the pulmonary artery, following the course of the rupture into the last-named vessel. *F*. Continuation of the same catheter into the right ventricle through the orifice of the pulmonary artery. A section was cut out of the catheter in order to show position of aortic cusps. *G*. Catheter passed from the aneurysmal cavity through the thrombus and pericardium and entering the pericardial cavity into which the aneurysm ruptured. There were clinical and pathologic reasons for believing that the rupture into the pulmonary artery was old—probably several weeks. The rupture into the pericardial cavity was recent, and had been the immediate cause of death. *H*. Inferior thyroid artery. *I*. Wall of aneurysm. *J*. Laminated thrombus, through the center of which the circulation had been maintained. Above the leader from the letter *J* are shown four slit-like areas that contained dark clots of blood (red thrombi). The remainder of the thrombus was white.

The morbid histology of this stage is characterized by a reduction in the size, and a less crowded condition, of the subserous capillaries,

[1] See Cerebrospinal Meningitis.

[2] "Arch. de Med. exper. et d'Anat. path.," Jan., 1905, p. 54.

which have been largely relieved by the escape of those materials entering into the formation of the exudate. The layer of fibrin, on section and in teasings, contains abundant leukocytes and a few erythrocytes; the endothelial cells will be seen desquamating, the process, at points, being laminated; masses of these elements occur far up in the fibrinous layer.

The morbid physiology of the exudative stage is manifested by the altered functional activity of the encumbered viscus, or viscera, and the results of the toxic action of metabolic products derived from the bacteria and tissues. If an abundant exudate be present, pressure will influence the action of the environed organ and will mechanically impede its function. Friction sounds, when previously present, disappear if the exudate be sufficient to force the two ayers apart and the fibrin covers the roughened serous surfaces. The fever may be kept up by the absorption of the metabolic products; these also induce, not uncommonly, phenomena not usually due to pyrexia alone: *e. g.*, suppression of excretion and nervous symptoms. The fibrinous exudate may so conceal and obstruct access to the lymphatic and vascular exits as to preclude resorption of the serum or its pyrogenous constituents, and hence no systemic phenomena due to their absorption will be manifest. When percussion and auscultation are permissible, as in pleurisy, pericarditis, and peritonitis, the phenomena associated with the presence of solids or liquids in the affected cavities may be found: *e. g.*, dullness.

Fig. 233.—Vertical Section through an Inflamed Serosa after the Formation of the Fibrinous Exudate.—(*Schmaus.*) × 250 diameters.

a. Subpericardial fat. *b.* Swollen membrane, the surface of which is contiguous to and blends with the overlying fibrinous deposit *c.* *c.* Layer of fibrin in which are numerous leukocytes, *d*, and into which, at *e*, are developing blood-vessels.

Exactly how long the stages of engorgement and exudation may last can not be approximated with any degree of accuracy; their duration varies, the conditions inducing the variation being but indifferently understood; the cause, the severity of the attack, the condition of the patient, whether weak or strong, are undoubted determining factors. The stages may be prolonged or brief, and just what determines this can not always be definitely stated; sooner or later, if the patient survives, repair proceeds as follows:

In this stage the connective-tissue cells, and possibly some of the mononuclear leukocytes, present in the wall of fibrin proliferate and convert the layer into embryonic tissue; young blood-vessels are developed from the subserous layers, and lymphatic connection is re-established. The facility with which young blood-vessels shoot up into the new tissue is marvelous, and to the rapidity with which this process of organization develops, modern surgery owes many of its most brilliant achievements.

FIG. 234.—INTERCOSTAL MUSCLE.

Transverse section, from a case of epipneumonic pleurisy, showing dissociation of fibers, interfascicular leukocytic infiltration, and slight fibrin formation. Tissue fixed in Zenker's fluid; hematoxylin and eosin stain.
A, A, A. Granular and fragmented muscle-fibers. *B*. Accumulation of leukocytes and fibrin around and extending between the muscle-fibers. In some areas the change is more marked than in others, and at points many polymorphonuclear leukocytes can be seen.

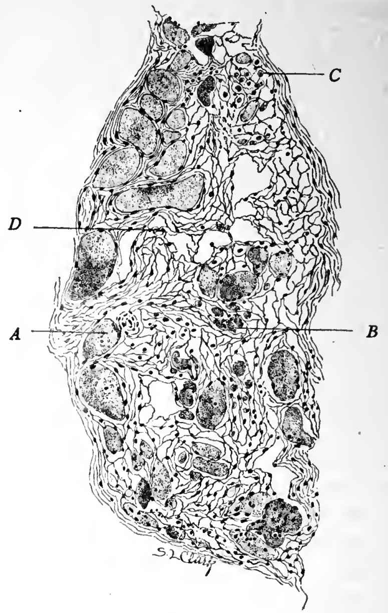


FIG. 235.—INTERCOSTAL MUSCLE, CASE OF EMPYEMA.

Transverse section, from a case of suppurative pleurisy of several months' duration, showing advanced fibrosis and lipomatous change. Tissue fixed in Zenker's fluid; hematoxylin and eosin stain.
A. One of several granular fibers, some of which are fragmented and undergoing absorption. *B*. A small group of greatly shrunken muscle fibers. *C*. Relatively large mononuclear cell, not very abundant, but commonly associated with fibroblastic elements. *D*. The leader from this letter passes between two imperfectly presented fat bodies, a number of which are present in the newly forming or formed fibrous tissue. The fat content is scanty in the particular field from which this drawing was made.

The leukocytes and young proliferating connective-tissue cells, the progeny of the endothelial lining, constitute a small, round-cell mass known as embryonic or formative tissue; when the young blood-vessels permeate this structure,—in other words, when it becomes vascularized,—it is known as granulation tissue. The next step is the organization of this into fibrous connective tissue, which, becoming smoothed, gives a surface functionally normal; but as all organizing tissue manifests a ten-

dency to contract, grave results may ensue in the structures beneath. Following meningeal inflammation, pressure upon nerves leaving the brain may, by constriction, lead to degeneration and entire loss of conducting power, paralyses, blindness, or deafness being thereby produced. Over the lung the contraction may preclude re-expansion and favor the continued presence of the serous exudate. A band around the intestine may cause narrowing, and eventually obstruction. In the pericardium, however, it is not believed that the contraction does sufficient harm to merit consideration. If adhesions attach the heart to contiguous structures—chest wall, diaphragm, or mediastinum—the expansion of the organ may be little influenced, the principal danger lying in the fact that, at each contraction, the attached, often rigid structures pull upon, and resist reduction in the size of the heart necessary in order to empty its cavities. Riesman[1] believes that pericarditis is more damaging to the heart than is endocarditis.

Adhesions between two layers of a serous membrane—*e. g.*, the pericardium—are brought about by the two fibrinous surfaces coming together at any stage of the inflammation before organization is well under way. In the recent state the fibrinous layers, if brought in contact, are at once agglutinated, and it is not improbable that, in the embryonic tissue stage of the inflammation, or even when vascularization is well advanced, cohesion of the two surfaces, followed by an organized adhesion, is possible. After agglutination of the fibrin-covered surfaces, or in the later stages when the contact is intimate and prolonged, the young blood-vessels anastomose and pass from one side to the other, organization into fibrous tissue ensues, following the lines already indicated, and an adhesion is the result.[2] The constant movement of the heart probably precludes general union of the pericardial layers at a

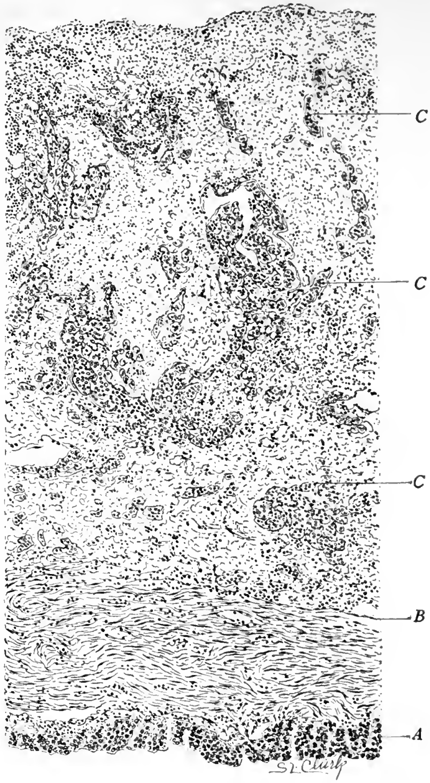


Fig. 236.—Pericardium (over Auricle); Acute Serofibrinous Pericarditis Engrafted on a Serosa the Site of Past Inflammations.

A. Portion of auricular myocardium. *A* to *B*. Greatly thickened pericardium composed of relatively dense fibrous tissue, upon the surface of which is attached the product of a recent inflammation; the latter is composed of fibrin and formative elements, the former having largely disappeared. *C*, *C*, *C*. Three young vessels; many others can be seen in the drawing. The surface, above the upper *C*, has not been reached by the young vessels.

[1] "Amer. Jour. of Med. Sci.," Sept., 1904, p. 466.
[2] Compare with union by first intention, p. 301.

single attack, but in the pleura it is not improbable that the entire sac may be obliterated by the first pleurisy that occurs, especially if the process be of the plastic type. Whether adhesions form or not, the serous membrane remains permanently thickened. Into this new tissue lime salts or fat may be deposited. In the former instance the condition is known as *calcification;* in the latter, as *fatty infiltration.* When the inflammatory process is associated with the deposit of lime salts, the terms **pleuritis petrificans, pericarditis petrificans,** or **calcifying serositis** may be applied.

An opportunity to study the formation of adhesions is afforded in almost all surgical operations upon serous surfaces. When a wound involves the intestine the two serous surfaces are brought together by sutures; along the line of contact an exudation of liquor sanguinis and the migration of leukocytes occur; the former separates into fibrin and serum, the fibrin forming a temporary cement and binding the two apposed surfaces together. The rapidity with which this preliminary agglutination occurs is well illustrated in the case reported by Oliver,[1] in which, after five hours, the sutured intestinal wall had formed a water-tight joint. Embryonic tissue is formed, followed by granulation tissue, and later by a cicatrix that unites the surfaces along the line of suture. This cicatrix is an adhesion, the histology and mode of development of which are practically identical with the formation of adhesions in pericarditis, pleurisy, inflammations of tendon-sheaths, etc. The closing or obliteration of the sac for the cure of hydrocele is brought about by inducing an inflammation of the serous membrane and favoring adhesion of the walls by removal of the contents, thereby permitting collapse. The surgeon withdraws the contents and brings about an inflammation of the lining membrane by gently scratching the serous surface or by injecting an irritant, such as iodin. Such injury is followed by redness (hyperemia), the formation of a fibrinous exudate, and agglutination of the collapsed walls; proliferation of the connective-tissue cells leads to repair, just as indicated in the foregoing description of adhesion formation. In this case adhesions are expected, and, as in the union of two serous surfaces when sutured, the success of the operation depends upon the development of new fibrous tissue through which permanent adhesion and obliteration of the serous cavity are secured.

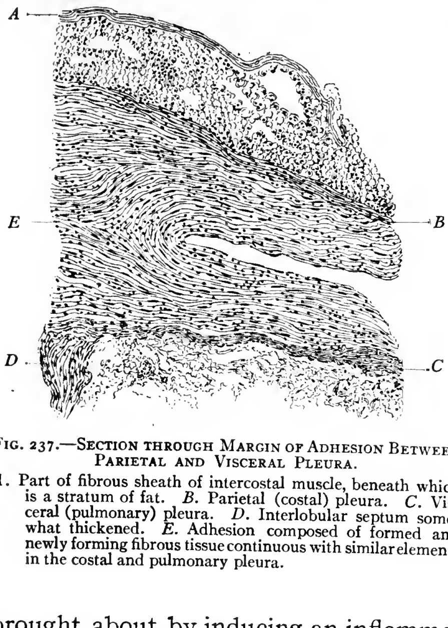


FIG. 237.—SECTION THROUGH MARGIN OF ADHESION BETWEEN PARIETAL AND VISCERAL PLEURA.

A. Part of fibrous sheath of intercostal muscle, beneath which is a stratum of fat. *B*. Parietal (costal) pleura. *C*. Visceral (pulmonary) pleura. *D*. Interlobular septum somewhat thickened. *E*. Adhesion composed of formed and newly forming fibrous tissue continuous with similar elements in the costal and pulmonary pleura.

[1] "Cincinnati Acad. of Med.," Jan. 28, 1901.

Suppurative serositis results from infection of a serous membrane by bacteria introduced from without, as by wounds and injuries, or from some body-cavity normally containing microorganisms, such as the alimentary canal, or is the result of extension of infection from a viscus covered by the serosa; sometimes the infecting germs reach the serous membrane by the blood-stream, and occasionally through the lymphatic vessels. Suppuration in the peritoneum (**pyoperitoneum**) is due to infection from some intra-abdominal viscus, as the appendix, perforated intestine, duodenum or stomach, infections of the gall-bladder and liver, abscesses of the spleen, kidney, pararenal structure, or abdominal wall; the bacteria may enter the peritoneum from the genito-urinary and reproductive organs. In the female the uterus and its appendages frequently constitute the atrium through which infection occurs. Hematogenous and lymphogenous infections occur, but are less frequent. Occasionally infection results from rupture of mesenteric or retroperitoneal lymph-nodes. It is to be remembered that by propagative infection bacteria may pass through the wall of a hollow viscus (intestine, gall-bladder, uterus, etc.) in the absence of any structural alteration that could be called a perforation. The peritoneum may be infected from the thoracic serosæ, or by wounds from without. Suppurative serositis affecting the pleura (**empyema, pyothorax, suppurative pleurisy**) commonly results from extension from the lung, particularly after pneumonia (especially in children), and in tuberculosis associated with cavity formation; less commonly the infection reaches the pleura from disease of the thoracic wall, esophagus, lymph-nodes, or other mediastinal tissue, or from a sub-diaphragmatic organ, as the liver, spleen, or stomach. Septic pulmonary infarcts and gangrene of the lung are sometimes causes; the pleura is occasionally infected from the blood-stream. The disease is common in children, particularly between the first and fifth and the eighth and ninth years. Bythell[1] is of the opinion that the condition is always secondary, and that the so-called primary cases are infections from undiscovered patches of pneumonic consolidation. Jurewitsch[2] attributes the so-called idiopathic empyemata to infection from a pulmonary lymphangitis. Penetrating wounds of the chest, and even blows and injuries without solution in the continuity of the thoracic wall, may give rise to empyema. Echinococcal disease in contiguous structures may suppurate and infect the pleura.

The bacteriology of empyema is essentially that of serositis.[3] The studies of Bythell, Foulerton,[4] Nathan,[5] Cotton,[6] and others may be epitomized in the statement that seventy-five per cent. of the empyemata in adults and about twenty-five per cent. in children are due to the streptococcus; seventy-five per cent. of the cases in childhood and twenty-five per cent. in adults are due to the pneumococcus. The other bacteria found in suppurative pleurisy are the usual pyogenic organisms to which reference has already been made.[7]

Suppurative pericarditis (**pyopericardium**) is usually the result of

[1] "Jour. of Path. and Bact.," March, 1904, p. 359, and July, p. 365.
[2] "Münch. med. Woch.," March 15, 1904, p. 480.
[3] See page 459.
[4] "Lancet," Aug. 17, 1901.
[5] "Arch. f. Kinderheilk.," 1904, Bd. xxxvi.
[6] "Boston Med. and Surg. Jour.," July 17, 1902, p. 63.
[7] See p. 459.

pneumonia, but may be associated with infection of any contiguous structure, particularly the pleura; the membrane may also suffer from infection beginning in some adjacent abdominal viscus. Occasionally pericarditis is secondary to suppurative lesions of the myocardium or endocardium, or due to hematogenous infection. I have seen it follow ulcerative lesions of the esophagus and suppuration of a contiguous lymph-node. Batten[1] observes that suppurative pericarditis is seldom suspected, rarely diagnosed, hardly ever treated, though it is present in three per cent. of all dead children; the accuracy of this statement can not be doubted, and my experience indicates that, so far as recognition of the condition is concerned, it applies to adults about as well as to infants.

Suppurative meningitis may result from hematogenous infection, the extension of suppurative processes from the skull or vertebræ, and wounds and injuries that involve the bony case surrounding the brain and cord. Maragliano[2] has shown that infection may occur from the nasal and frontal sinuses. The condition frequently is associated with middle-ear disease.

Suppurative arthritis, thecitis, and **bursitis** usually result from infected wounds or bacteria brought by the blood-stream. Joints are frequently infected from the adjacent bone.

Morbid Anatomy of Suppurative Serositis.—There has been considerable discussion as to whether purulent inflammations of the serous membranes were preceded by the occurrence of serofibrinous exudates. My own belief is that in most of these cases, even when primarily suppurative, an exudate containing serum or fibrin is practically always formed; Beattie's studies support this view, and certainly at autopsy suppurative serositis without the presence of distinct fibrin-bearing areas is an exception. The chief anatomic difference between the suppurative inflammation and the typical serofibrinous serositis is the enormous number of polymorphonuclear leukocytes present in the former. Fluidification[3] of the exudate and accumulation of pus cells progress during the activity of the infection. Swelling and, in chronic cases, proliferative changes are constantly observed in the subserosa. The latter processes, with attempted organization of the deeper layers of the exudate, result in the formation of an investing stratum of suppurating granulation tissue resting upon the fibrous, edematous, and hyperemic subserosa. In the earlier stages before the fibrous tissue formation is marked this structure is called a *pyogenic membrane*. Structurally, such a membrane is composed of cellular elements not unlike those found in the wall of an abscess (p. 295); later, the free surface continues to be rich in leukocytes, and therefore largely cellular. Within this cellular accumulation the conflict between the bacteria and the cells continues, and is manifested by the associated phagocytosis, necrosis, and pus-formation. Below this wall there is sooner or later developed a layer of fibrous tissue. As this cicatricial structure, in conjunction with its overlying cellular layer, presents a certain resistance to the further invasion of the underlying tissues by the bacteria,

[1] "Brit. Med. Jour.," Sept. 7, 1901.
[2] "Gaz. osped et Clin.," 1905, No. 19.
[3] The processes operative in the liquefaction of inflammatory exudates and the formation of pus will be found discussed on p. 294.

Park proposed for it the name *prophylactic membrane.* The thickening may exceed one centimeter; the membrane is usually tough, the surface soft and downy, and bleeds upon the slightest injury. The deeper layer not infrequently contains calcareous material. In the suppurative inflammation of serous membranes the fever-producing element present in the noninfective forms has its activity augmented by the addition of the pyrogenous products of the pyococci.

The changes in the tissues contiguous to the suppurating serosa resemble those already described as occurring in the nonsuppurative forms of serositis. In the peritoneum the intestines dilate, the adjacent muscle degenerates, the lymphatics contain numerous leukocytes, and even the solar plexus shows alterations attributable to contact with the bacterial toxins. The absorbed poisons produce an intense toxemia which usually terminates in death. When the lesion is localized in the vicinity of the appendix, uterus, or other viscus, the absorbing surface is proportionately reduced, and the outlook is more hopeful. Such localized collections of pus may rupture into the general cavity and, by suddenly inundating the serosa, give rise to a violent toxemia and rapidly fatal general peritonitis; the dangers are essentially the same as if two or three hundred cubic centimeters of pus were injected into a normal peritoneum.

Empyema, in addition to the mechanical compression of the lung, endangers contiguous structures by the extension of the infectious process. A suppurative lymphangitis may traverse the lung, giving rise to irregular lines of purulent inflammation passing from the periphery to the hilum; a bronchus may be penetrated and the patient drowned in the pus, or the infectious matter disseminated in the opposite lung. Extension to the pericardium is not rare. The changes in the muscles and diaphragm are essentially similar to, but more marked than, those described on page 463 and shown in Fig. 143, page 251, and Figs. 234 and 235. Protracted suppuration of the pleura induces irreparable damage in the underlying lung, subjects the patient to the dangers of general sepsis and amyloid disease, and, should recovery ensue, the chest is frequently deformed and the spinal column may be bent, as a result of the thoracic wall sinking on the lung, which can not expand. Collapse of the chest wall is the only way that the empyema cavity can be obliterated. Sometimes the empyema is loculated; the pus cavity may be between the lobes (*interlobar empyema*), or at the base, the floor of the purulent collection being formed by the diaphragm. These cases often come to autopsy without the nature of the process having been suspected.

Putrid pleurisies are due to the presence of saprophytic bacteria in the pus of empyema. Guillemot, Hallé and Rist[1] have shown that the infection is practically always polymicrobic and that anaerobic bacteria are almost constantly present. The toxic processes accompanying such conditions are usually marked and reparative activity suppressed. In resistant individuals the infection often drags on for months or even years; the weakly succumb.

Suppurative pericarditis (pyopericardium) offers the same dangers to the heart as serofibrinous inflammation and exudates, and, in addition, two important possibilities. The toxic processes are much more intense, and, secondly, the myocardial alterations are more marked.

[1] "Arch. de Méd. exper.," Sept., 1904, p. 571.

The contiguous layer of the heart muscle often manifests advanced degeneration, and occasionally pus cells may be seen intercalated between the fibers. Rarely mediastinal abscess follows pericardial suppuration; the reverse is more frequent. Suppurative pericarditis seems more prone to calcific changes than suppurative pleurisy or peritonitis.

Inflammation of the serous membranes is sometimes accompanied by exudates that contain blood; to this condition the term **hemorrhagic inflammation** is applied. Hemorrhagic serositis occurs most commonly in connection with debilitating conditions, such as tuberculosis, asthenic states, cancer of the serous membrane, and, rarely, without any apparent cause. Trauma may lead to hemorrhage in the exudate. Tapping may rupture some of the delicate vessels of an organizing exudate, or withdrawal of the serous exudate may remove the support to the delicate newly formed capillaries, which rupture, and thereby give rise to blood in the fluid. The hemorrhagic phenomenon may show in the serum, or it may be manifested by petechiæ or areas of subserous rhexis. The hemorrhagic inflammations are most frequent in childhood, although not unknown at any age. The pleura is oftenest affected. The frequency of the hemorrhagic form of pleurisy is variously given by different writers: Lewin found the effusion hemorrhagic in 4 out of 50 cases; Reimer, five times in 121 autopsies; and Israel,[1] twice in 206.

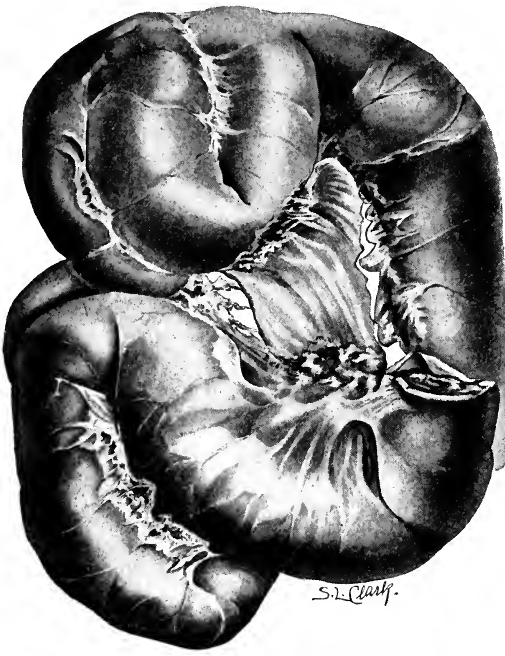


FIG. 238.—INTESTINE. CHRONIC ADHESIVE PERITONITIS.

In certain forms of **chronic serositis**[2] there occurs an inflammation, of a low order, characterized by a serous exudate

[1] "Jahrbuch für Kinderheilkunde," 1898, Bd. xlvii, No. 16.

[2] The literature of chronic inflammation of the serous membranes will be found in or may be traced from the following: Nicholls, see foot-note, p. 461. Harris, "Indurative Mediastino-pericarditis," London, 1895. Turk, "Wien. klin. Woch.," XVI Jahrgang, Nos. 37, 39. and 40. Eichhorst, "Deut. med. Woch.," April 17, 1902. Kelly, "Amer. Jour. of Med. Sci.," Jan., 1903, p. 116. Gibson, Bullmore and Conder, "The Practitioner," Feb., 1903, p. 213. W. Hale White, "Brit. Med. Jour.," March 7, 1903, p. 536. Pollard, "Lancet," March 28, 1903, p. 871. Brauer. Thirty-second German Surgical Congress, June 3 to 6, 1903. Schupfer, "Rif. Med.," March 2, 1904. Wetherill, "Jour. Amer. Med. Assoc.," March 5, 1904, p. 634. Scott, "Amer. Jour. of Obstetrics," Nov., 1904. Mouisset and Vallas, "Lyno Méd.," Feb. 5, 1905.

containing but few cells and a small quantity of fibrin. This type of inflammation should be called **chronic serous exudative serositis**. The pathologic process is due to persisting slight irritation and is seen in the joints as a result of loose cartilages; sometimes it follows minor injuries of the tendon-sheaths and bursæ. A similar condition is occasionally observed in the peritoneum, pleura, and pericardium, and it is probable that some cases are tuberculous. Benign tumors of the uterus, ovary, or other abdominal viscus may be attended by such a process. To the unaided eye the serous membrane frequently shows no gross lesion; there may be, at points, whitish or slightly opaque areas, particularly if the serosa has been subjected to friction.

Long-continued inflammation of the serous membrane, attended by the production of fibrin and serum—**chronic serofibrinous exudative serositis**—is rarely observed; sometimes, however, infection by organisms or slight virulence may give rise to such a process. By some observers the later stages of suppurative inflammation (p. 470) of the serous membrane, characterized by the production of a large amount of fibrinous exudate and pus, are included under the term chronic suppurative pleurisy, pericarditis, peritonitis, etc.

Chronic hyperplastic or **productive inflammation** of the serous membranes, also called **progressive hyaloserositis,** is attended by but little exudate often none, and is characterized by the production of a large amount of fibrous tissue which forms a distinct layer, sometimes 1 cm. to 2 cm. thick; the process may be patchy or diffuse. The amount of serum present in these cases is usually small. In some instances the tendency to adhesion is slight, while in others large areas, and sometimes all of the cavity, may be obliterated by complete fusion of the parietal and visceral layers of the affected serosa. W. Hale White refers to cases in which it is possible to remove the abdominal viscera intact, as a single mass, transverse section of which discloses the intestine held open by the thickened investing peritoneum. The liver and spleen are sometimes adherent to the abdominal wall and uniformly invested in a dense white layer of hyalofibrous tissue. In other cases adhesions are absent; the affected serosa is covered by a white or grayish-white fibrous tissue 2 mm. to 5 mm. in thickness and sometimes thicker; an organ may be completely invested in such hyalofibrous tissue, rendering the surface white or grayish-white, often resembling an iced cake—the "Zuckergussleber" of the German writers.

Often the peritoneum, pericardium, and pleuræ are affected, hence the name multiple or polyserositis. When the condition is restricted to one organ (spleen or liver), the term **fibrous capsulitis** is sometimes applied, although it is questionable whether true capsular inflammation is really a manifestation of this process. Histologically the thickened membrane possesses the structural characters of a chronic progressing inflammation. The new tissue is composed of lamellæ of hyaline fibrous tissue interspersed with formative cells in various stages of fibroblastic transformation; often the capsule of the organ may be distinguished from the new tissue on the surface, the latter appearing as an organized, superimposed stratum on a slightly altered capsule. The blood-vessels of the newly formed tissue are often surrounded by mantles of cells indistinguishable from small mononuclear leukocytes. The condition may or may not be associated with fibrous hyperplasia of the interstitial

tissue in the enveloped organ. There is no necessary relation between the two.

With regard to the cause of the condition we are almost totally ignorant. The anatomic changes and certain of the clinical phenomena indicate that the process depends upon the prolonged action of some irritant the nature of which is unknown. I am strongly inclined to agree with Nicholls, who is almost persuaded that the process is bacterial in origin. In some respects it resembles the chronic productive form of tuberculosis, and it is not impossible that some cases are due to the tubercle bacillus. The absence of anatomic tubercles, giant cells, and even inability to demonstrate bacilli, do not necessarily constitute conclusive proof of its nontuberculous nature. It is possible that the chronic productive serositis without adhesions may be different from the adhesive form, but the reasons for recognizing them as distinct processes do not appear convincing.

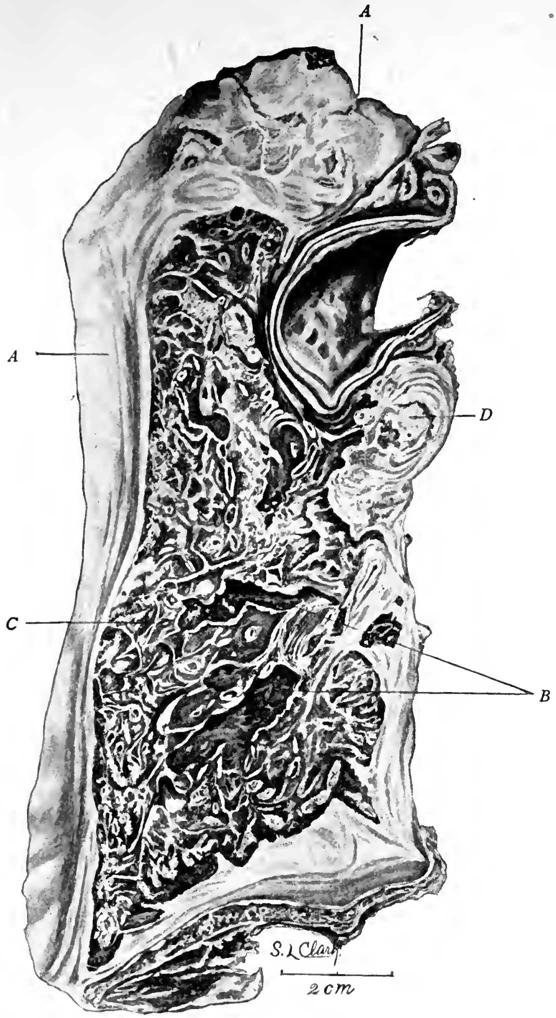


FIG. 239.—LUNG. CHRONIC INTERSTITIAL PNEUMONIA, BRONCHIECTASIS, HYALOSEROSITIS, AND A TERMINAL CATARRHAL PNEUMONIA DUE TO MIXED INFECTION BY THE TUBERCLE BACILLUS AND PNEUMOCOCCUS.

A A. Greatly thickened pleura. *B*. Dilated bronchi. *C* One of many broad strata of fibrous tissue irregularly traversing the organ. *D*. Large caseous lymph-node near hilum of lung and immediately adjacent to the aorta, a section of which is shown just above. The aorta is the seat of slight atheroma.

Strongly resembling the foregoing are **pericardiomediastinitis,** or **mediastinopericarditis,** and **pericarditis externa,** which are closely allied, if not identical conditions. The names given are applied to processes characterized by a chronic indurative inflammation extending from

the pericardium into the mediastinal tissues, which often become firm and resisting and closely attached to the sternum and costal cartilages. The condition may or may not be associated with the ordinary form of pericarditis, which, for purposes of distinction, is called **pericarditis interna.** When an inflammation of a serous membrane terminates in adhesions which firmly unite the apposed serous surfaces, the process is sometimes called obliterative, and hence it is possible to speak of obliterative pleurisy, obliterative pericarditis, obliterative peritonitis, etc.; such manifestations are also called chronic adhesive inflammations.

In addition to the foregoing forms of chronic pericarditis, it is necessary to recognize certain lesions which are the results of past acute inflammatory conditions; by some these are grouped with the chronic inflammations. In some cases it is evident that the inflammation began with an acute process which continued, and at the time of examination had lost all of its acute characters, but is continuing as a chronic lesion. This type belongs with the chronic forms described above. In other cases the process has long ceased to be active, there is no evidence of progression, the alterations remaining exactly as they were left when the active stages of the acute process subsided. The condition present may be that of: (1) Partial or complete adhesion; (2) large masses of fibrin whipped off in the serum may not have undergone absorption, but sometimes are perpetuated as caseous or semisolid collections too large to be vascularized; (3) caseous areas resulting from the absorption of the fluid portion of a past pus collection or from tuberculosis of the membrane; (4) calcareous masses in the newly formed inflammatory tissues.

Tuberculosis of the serous membranes,[1] like tuberculosis elsewhere, is manifested by the occurrence of many lesions, some of which bear no resemblance to the others. It may be acute or chronic. The source of the infection is usually some organ covered by the serosa or some contiguous structure from which the bacilli reach the membrane. In the peritoneum, tuberculosis of the intestine, lymph-nodes, uterus or its appendages, or the abdominal wall (including the vertebræ) may infect the serosa. The cases of alleged primary tuberculosis of the peritoneum must be regarded with suspicion. According to Bottomley,[2] Borschke observed primary infection once in 226, and Munsterman once in 46 cases. An acute miliary tuberculosis of the peritoneum may result from a hematogenous dissemination of the bacillus, and occasionally the peritoneum is infected from the thoracic serosæ. Tuberculosis of the pleura is usually due to infection from the underlying lung, although it has been suggested that the bacteria may enter the apex from the cervical lymph-nodes, the latter infected by way of the tonsils and pharynx. Tuberculous pleurisy secondary to mediastinal, esophageal,

[1] MacCallum, "Bull. of Johns Hopkins Hosp.," 1901. W. Hale White, "Clinical Jour.," Aug. 21, 1901. Nicoloff, Thèse de Paris, 1904. Thayer, "Bull. of Johns Hopkins Hosp.," May, 1904, p. 149. Scagliosi, "Deut. med. Woch.," June 9, 1904. Norris, "Univ. of Penna. Med. Bull.," July–August, 1904. Ipsen, "Virchow's Arch.," Sept. 1, 1904, Bd. 177, p. 570. Longyear, "Amer. Jour. of Obstetrics," Nov., 1904. Rosenbach, Nothnagel's Encyclopedia, American edition, "Diseases of the Bronchi, Pleura, and Lungs," 1903, p. 962. Cornet, Nothnagel's Encyclopedia, American edition, "Tuberculosis, Acute and Chronic Miliary Tuberculosis," 1904, p. 195.

[2] "Med. and Surg. Reports of the Boston City Hospital," 1900, eleventh series.

and vertebral lesions is less common. This statement is made with the understanding that infections from the peribronchial lymph-nodes belong with those due to extension from the lung and not with those arising from the mediastinum. Hematogenous infection of the pleura occasionally occurs.

Tuberculous pericarditis is rarely, if ever, primary; usually the infection is an extension from tuberculosis of contiguous structures, especially the lymph-nodes near the base of the heart. The pericardium may also be affected from the pleura, adherent lung, mediastinal tissues, esophagus, and peritoneum. In a large percentage of cases pericarditis is due to hematogenous infection. Sometimes the lesion is a part of an acute general miliary tuberculosis. The last statement also applies to tuberculosis of the meninges. Meningeal infection may occur from contiguous structures, such as the bodies of the vertebræ, middle ear, or other foci in the bony walls enclosing the brain and cord. Tuberculous thecitis may be due to inoculation, but, in the large majority of cases, is an infection from the blood. The same is true of bursitis due to the tubercle bacillus. In the joints, tuberculosis is commonly the result of extension from contiguous bone. There can be no doubt that in all these cases colonization of the tubercle bacillus is favored by trauma or any other antecedent condition which weakens the resistance of the tissues.

Morbid Anatomy of Tuberculosis of the Serous Membranes.—It is possible to recognize acute and chronic types of the affection; the former will be considered first. An eruption of tubercles in a serous membrane may be attended by the accumulation of a clear serum in the cavity and no recognizable fibrinous deposit on the surface of the membrane. In such cases the tubercles appear to be in the subserosa, and usually are easily recognized as grayish-white dotlets scarcely a millimeter in diameter; as a rule, they are palpable. These are the cases which, when the peritoneum is involved, appear to be greatly benefited by operative procedure. In other cases of tuberculous serositis the affected membrane is covered by a shaggy coat of fibrin indistinguishable from that seen in the ordinary type of acute serofibrinous pleurisy or pericarditis. Norris found this form in seven of the eighty-two cases of pericarditis which he studied. The quantity of fluid is often excessive; the peritoneum may contain four to eight liters, and the pleura half as much; Hirtz reported a case in which 2700 c.c. of blood-stained serum was present in the pericardium. Sometimes the effusion is hemorrhagic and distinctly fibrinopurulent exudates are occasionally encountered.

The chronic forms of tuberculous serositis may be sequences of the acute, but often arise insidiously. A chronic serous inflammation, or at least a chronic inflammation of the serosa with an abundant, clear, straw-colored, serous exudate, occurs particularly in the peritoneum; manp patients recover from this form. In another type of the affection the structural changes resemble those of a chronic productive adhesive serositis. Multiple adhesions form, or, in some cases, the cavity of the affected serosa may be obliterated by firmly organized fibrous tissue in which but few tubercles and no caseous areas can be demonstrated. Ipsen has been able to collect twelve cases of tuberculosis in man possessing the anatomic characters of the bovine form of the affection. In

some of these instances the lesions on the serosæ resemble the changes seen in cattle, which consist of nodular masses of fibrous tissue with little or no tendency toward caseation. The pedunculated and sessile nodules described by MacCallum resemble this type. In still another group of tuberculoses large nodules with caseous centers and fibrous peripheries are irregularly distributed over the affected serosa. In the case of tuberculous mediastino-pericarditis reported by Ellis[1] the mediastinal tissues, pericardium, and heart were fused in a single mass, and large, caseous nodules surrounded the bronchi, trachea, and large vessels. The cavities of both pleuræ were obliterated. The caseous nodules varied in diameter from 0.2 cm. to 2 cm., and at points the tuberculous process involved the myocardium. It is interesting to note that in this case the examination of a large number of sections failed to disclose a single characteristic tubercle or even a giant cell;

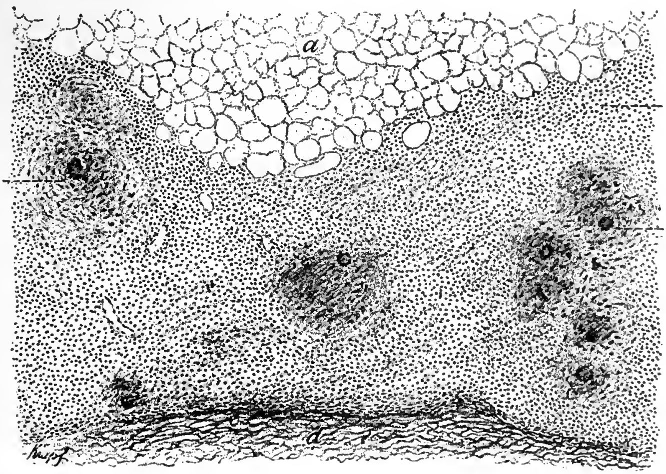


FIG. 240.—ACUTE TUBERCULOUS PERICARDITIS, VERTICAL SECTION OF INFLAMMATORY EXUDATE.—(*Schmaus.*) × 250 diameters.

a. Subpericardial fat. *b.* Layer of granulation tissue that extends to the layer of fibrin, *d.* *c, c.* Tubercles containing giant-cells. Other tubercles are shown, in some of which degenerative changes are beginning to evince themselves.

the new tissue consisted of lymphoid and fibrous structures in which caseation had run riot. Tubercle bacilli, however, could be demonstrated.

Cytodiagnosis offers aid in determining the character and origin of exudates in the serous cavities. The method is discussed on p. 291.

Actinomycotic serositis has been reported, but the condition is rare; it is usually secondary to actinomycosis of some viscus covered by the peritoneum or pleura. The lesion is commonly chronic and the fungus may be demonstrated in the exudate or granulation tissue. Actinomycotic pleurisy is usually due to infection from the underlying lung; the same is true of the pericardium; less frequently the latter structure is involved secondarily to the mediastinal tissues. Actino-

[1] "Proceed. of Path. Soc. of Phila.," Jan. 29, 1904.

mycotic lesions of the serous membranes are often strictly localized to the area in which infection occurred.

Various serous membrane inflammations have been attributed to syphilis, and in the meninges the chronic productive **meningo-encephalitis** is clearly of syphilitic origin.[1] Eruptions of **leprous nodules** may occur on the pleura and are usually secondary to pulmonary infection.

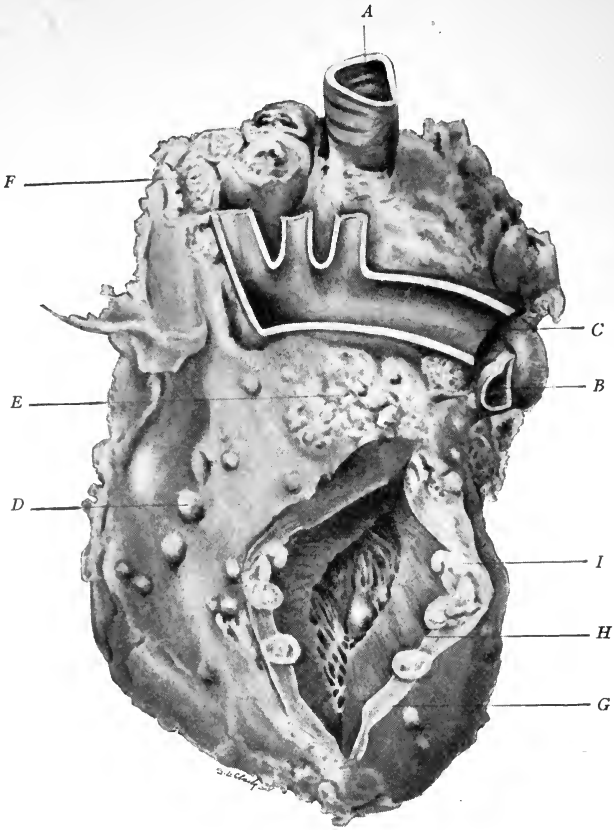


FIG. 241.—CHRONIC, ADHESIVE, INDURATIVE, AND CASEOUS TUBERCULOUS MEDIASTINOPERICARDITIS. HEART AND ADJACENT MEDIASTINAL STRUCTURES. (Four-ninths natural size.)

A. Trachea slightly distorted by pressure. *B*. Left bronchus, compressed by enlarged peribronchial lymph-nodes. *C*. Aorta; the arch is displaced to the right, the middle of the arch is elongated largely at the expense of the descending portion. It is probable that a large part, but certainly not all, of this distortion is postmortem. *D*. One of several caseous nodes on the mediastinal aspect of the pericardium; some of these nodules are indistinguishable from caseous masses that have arisen in the pericardial synechia. *E*. Area of caseous tuberculosis, occupying fissure between the left auricle and corresponding ventricle. *F*. Caseous mediastinal (peritracheal) lymph-nodes. G. Thickened and adherent parietal layer of the pericardium. *H*. Thickened visceral layer of the pericardium (epicardium). The space between *F* and *G* is occupied by firm, grayish, slightly hyaline fibrous tissue in which are embedded many caseous areas. *I*. Caseous mass extending into the myocardium. Even in this short incision, through the lateral wall of the left ventricle, several points of myocardial invasion can be seen.

Air in the serous cavities is always regarded as a source of danger

[1] See Diseases of the Nervous System.

and is usually followed by evidences of infection. It was once believed that air was an irritant capable of producing inflammation. Clinical and experimental evidence shows that sterile air gives rise to no structural alteration in the serosa, although the viscera (especially the lung) may be profoundly influenced by the pressure induced by the gas. Lundie[1] reported an instance where air was present in the pleura and pericardium on at least two occasions and at no time was there any evidence of inflammation. Air is often introduced into the serous cavities for diagnostic or therapeutic purposes, and if sterile, does no harm. Gas, present in most instances, is the result of wounds admitting air from the outside, or traumatic ruptures or penetration of some hollow viscus; in either case the gas is accompanied by infection which rapidly produces inflammation that is usually suppurative. In some cases ulceration, gangrene, or other pathologic processes perforate the serous covering of a hollow viscus, admit air and infection, and give rise to serositis. Gas may arise in the serous cavities as a result of infection by aerogenic bacteria. The organisms present are usually the Bacillus aerogenes capsulatus or other gas-producing bacteria, and in some cases the colon bacillus alone. May and Gebhardt[2] suggest for this type the names **zymotic peritonitis, zymotic pneumothorax,** and **zymotic pneumopericardium.** This form is occasionally seen in the peritoneum, but most of the peritonitides associated with the presence of air are due to perforation of the stomach or intestine. Most of the cases of pneumothorax are the result of tuberculosis of the lung. Biach found that of 918 cases of pneumothorax, 715 were due to tuberculosis, 65 were associated with gangrene of the lung, 45 accompanied empyema, and 32 followed trauma. Fussell and Riesman[3] were able to collect 56 cases thought not to be tuberculous; many of these followed trauma. Bovaird[4] reported 2 cases of pneumothorax resulting from rupture of areas of bronchopneumonic consolidation. Two others were due to ruptured abscess and the fifth was supposed to have resulted from the bursting of an emphysematous bleb. The condition sometimes follows violent respiratory effort, as coughing, particularly in pertussis.[5]

Pneumopericardium is almost always the result of penetration of the sac from without. Of the 38 cases collected by James,[6] 4 were thought to be due to infection by gas-forming bacilli; in 7 the perforation was in the esophagus and in two gastric ulcer penetrated the pericardium. In the case reported by Müller pyopericardium perforated the lung. In most cases infection accompanies the entering air, and pneumopericardium is converted into a pyopneumopericardium.

Hemopericardium, hemothorax, and **hemoperitoneum** are usually due to trauma, particularly crushes and penetrating wounds of the cavities. The condition may also result from ruptured aneurysm, and a variable

[1] "Edinburgh Med. Jour.," 1891, No. 1805.
[2] "Deut. Arch. f. klin. Med.," lxi.
[3] "Amer. Jour. of Med. Sci.," Aug., 1902, p. 218.
[4] "Arch. of Pediatrics," Nov., 1903.
[5] For fuller literature concerning pneumothorax consult Edmunds, "Brit. Med. Jour.," Nov. 21, 1903, p. 1322. Weber, "Zeit. f. Tuberk. u. Heilstw.," vol. iv, No. 6. Trask, "Jour. Amer. Med. Assoc.," March, 5, 1904, p. 641. Emerson, "Johns Hopkins Hospital Reports," 1903, vol. xi, pp. 1 to 445.
[6] "Amer. Med.," July 2, 1904, p. 23.

quantity of blood may be found mixed with the contained serum in scurvy, pernicious anemia, hemorrhagic septicemias, purpura, phosphorus poisoning, leukemia, and allied dyscrasias. In the latter group of cases petechiæ, and subserous hemorrhages of a larger size, are usually present.

Tumors of the serous membranes may be primary or secondary; the former may be benign or malignant. Most of the benign tumors are situated in the omentum, in which myxoma, lipoma, fibroma, chondroma, and even osteoma may occur. Hellier[1] reports a lymphangioma of the omentum and peritoneum which simulated ovarian tumor. It is probable that the congenital multilocular cystoma of the omentum observed by Young,[2] and a similar case reported by Hearn,[3] were of this type. Important among the abdominal tumors are the **retroperitoneal neoplasms**[4] and **cysts.** In this location, myxoma, lipoma, and sarcoma occur; Steele has been able to collect ninety-six cases belonging to the last group. Aside from the cysts arising from the solid viscera of the abdominal cavity, (1) serous, (2) blood, (3) chyle, (4) dermoid, and (5) parasitic cysts are sometimes observed.[5] In the case reported by Richardson the cyst contained eight pints of milky fluid. Liquid accumulations in the lesser omental cavity are sometimes called pseudo-cysts of the abdomen. Hydatids are the most common of the parasitic cysts, although cysticerci are also observed.

The most frequent primary tumor of the serous membrane is **endothelioma.**[6] This may give rise to distinct nodules, but frequently is a diffuse, flattened growth resembling the thickening produced by chronic hyaloserositis. The pleura is usually involved; the meninges of the brain and cord are second in point of frequency; the tumor is not common in the pericardium or peritoneum; it sometimes affects the bursæ and tendon-sheaths. There has been considerable discussion as to whether it arose from the surface cells of the serosa or from the endothelium of the lymph-vessels. Histologically the structure so closely resembles the alveolar types of cancer that many of these neoplasms are reported as instances of primary carcinoma of the serosa. The resemblance of the process to chronic inflammation of the serous membranes is intensified by the occurrence of exudates, which are usually hemorrhagic, or rapidly become so. The malignancy in different cases varies; sometimes life is prolonged for years, and in other cases the condition terminates fatally in a few months. The tendency to metastatic deposits is usually slight.

The **secondary tumors of the serous membranes** may be carcinoma-

[1] "Brit. Med. Jour.," Nov. 12, 1904, 1311.
[2] "Lancet," Jan. 21, 1905, p. 157.
[3] "Annals of Surgery," 1897.
[4] Adami, "Montreal Med. Jour.," 1897, vol. xxv. Douglas, "Jour. Amer. Med. Assoc.," March 26, 1898. Steele, "Amer. Jour. of Med. Sci.," March, 1900, and June, 1904.
[5] For literature of these cysts see Blum, "Centralbl. f. d. Granzgebieten d. Med. u. Chir.," 1902, vol. v. McMurtry, "N. Y. Med. Jour.," Dec. 31, 1904, p. 1256. Richardson, "Boston Med. and Surg. Jour.," Feb. 9, 1905, p. 151.
[6] Scagliosi, "Deut. med. Woch.," 1904, xxx, 1715, No. 47. Hilber, "Jahrbuch. f. Kinderheilk.," Bd. 59, H. 3. Bassoe, "Trans. of Chicago Path. Soc.," Nov. 9, 1903, p. 31. Nager, "Zieg. Beitr.," 1904, xxxvi, H. 1. Unger, "Wien. klin. Woch.," Dec. 24, 1903, p. 1457. Bonheim, "Münch. med. Woch.," April 26, 1904, p. 741. Adler, "N. Y. Acad. of Medicine," Oct. 20, 1904.

tous or sarcomatous, and are usually the result of extension from a neoplasm of some viscus within the affected cavity or in the wall of the latter. In some cases the secondary nodules are distributed over the serosa as minute elevations resembling warts; this condition may simultaneously affect all of the serous cavities of the trunk. When due to cancer, it is called **carcinosis,** and when the new growth is sarcoma, the term **sarcomatosis** is applied. Colloid cancer of the peritoneum is usually secondary to a primary growth in the alimentary canal, although Parkinson[1] and others have reported instances in which the growth was primary. In Parkinson's case the patient was twelve years old, at which age the disease is exceedingly rare.

[1] "Soc. for the Study of Disease in Children," May 15, 1903.

CHAPTER VI.

VASCULAR SYSTEM.

HEART.[1]

Normal Structure.—The heart is essentially a hollow muscle divided by partitions into two distinct sides, between which, normally, there is no communication; each side is further divided by a perforated septum into two cavities, known respectively as an auricle and a ventricle. The opening through which the auricle communicates with the ventricle on each side, called the auriculoventricular opening or orifice, is guarded by valves that open toward the ventricle; on the right side the valve is known as the tricuspid, on the left, as the mitral. The right ventricle communicates with the pulmonary artery and the left ventricle with the aorta, the two orifices being guarded by valves opening toward the vessels. These valves are each composed of three cusps, crescentic or semilunar in outline, and known as the semilunar valves of the pulmonary artery and of the aorta respectively. The exterior of the heart is covered by the pericardium, to which reference has already been made (serous membranes, p. 452); the interior is lined by a flattened layer of connective-tissue cells (endocardium) applied almost directly to the cardiac fiber, with but little, if any, loose connective tissue intervening; the valves are composed of two layers of the endocardium, reinforced by fibrous tissue, in which are a few elastic fibers. The valves of the right side, having less work than those of the left, are much the thinner, containing relatively less fibrous tissue. The endocardium, including most of the tissue that enters into the formation of the valves, is nonvascular, probably receiving its nutrition from the blood flowing over it. The cardiac muscle is of the striped variety, but differs from voluntary striped muscle; the fibers are usually said to possess no sarcolemma, and they inosculate by branched filaments, passing from one to another; there is no bundling of the fibers, and the individual elements are smaller than those of the purely voluntary muscle. Marceau[2] has shown that the mammalian heart possesses a higher, and more complicated, development than the heart of some other vertebrates. Nourishment for the organ is supplied by the coronary arteries, the circulation in which is in some respects peculiar. The usual teaching that these are terminal vessels is not correct, although the anastomosis between the two trunks is never free; in some hearts there is no communication between the branches of the right and left coronary arteries. Galli[3] has shown that, in many organs, the anastomosis is present, although never abundant. Meigs[4] believes that the

[1] For method of removing the heart and completing its dissection see pp. 11 and 12.

[2] "Ann. Sc. nat." Serie 8 Zool., vol. xxix, 1903, p. 199.

[3] "Münch. med. Woch.," July 7, 1903, p. 1146.

[4] "Proceed. of the Path. Soc. of Phila.," 1898, p. 186; references to earlier papers.

capillaries actually enter the muscle-fibers. The connective tissue of the normal myocardium is scanty and, except in the vessels, the amount of elastica is so small as to be scarcely demonstrable.

Size of Normal Heart.—The heart is about the size of the fist of the individual; its weight in the male varies between 285 gm. and 450 gm. (10 and 15 ounces), with a mean between 340 gm. and 390 gm. (11 and 13 ounces). The heart of the adult female weighs between 200 gm. and 400 gm. (7 and 13 ounces); mean, between 285 gm. and 300 gm. (9 and 10 ounces). The taller the ind vidual, the heavier the heart. In forming an estimate as to the normal weight of the heart, the size of the body and the amount of work required of the organ must be taken into consideration. The laborer weighing 80 kilos will almost certainly possess a heart weighing more than that of a clerk whose body-weight is the same. The relation between the cardiac and body-weights is not sufficiently constant to afford a basis for a positive opinion in a doubtful case. There are so many factors to be considered, the work, the nutrition, the age, the height, the sex, etc., that no arbitrary rule can be laid down to fit all conditions. The observer must weigh all obtainable facts and formulate his conclusion afterward; even then he may be in doubt in certain cases. The left ventricular wall is about 1.25 cm. ($\frac{1}{2}$ of an inch) in thickness, the right about 0.4 cm. ($\frac{1}{8}$ of an inch). Measurement alone affords insufficient evidence upon which to base an opinion as to the presence or absence of hypertrophy; the wall of a widely distended, hypertrophied heart may be thinner than the contracted normal myocardium. The ventricular wall is thickest at its middle and thinnest at the apex.

DIAMETERS OF CARDIAC ORIFICES.—(*After Hamilton.*)

	Male.			*Female.*		
	Greatest.	Least.	Average.	Greatest.	Least.	Average.
	Inch	Inch	Inch	Inch	Inch	Inch
Aortic,	1.3	0.9	1.0	1.0	0.8	0.9
Mitral,	1.8	1.1	1.4	1.5	1.0	1.2
Pulmonary Artery,	1.5	1.0	1.2	1.3	1.0	1.1
Tricuspid,	2.2	1.3	1.8	1.7	1.4	1.5

The taller the subject, the larger the orifices.

MALPOSITION OF THE HEART.

(A) CONGENITAL.

1. **Cervical Heart.**—Heart in the neck; the condition may be complete or partial, and is more frequent in the lower animals than in man.

2. **Abdominal Heart.**—Through faulty development of the diaphragm the heart may sink into the abdominal cavity; usually a fetus so affected dies, but Holt's patient was five months old and appeared otherwise healthy. Occasionally, the diaphragm does not develop immediately under the pericardium, and when the heart does not sink through the opening, an abdominal viscus may ascend into the pericardium, a result induced by the difference between the pressures within the two

cavities. When there is an opening in the diaphragm and any of the abdominal viscera enter the thoracic cavity, the changed relations and altered pressure practically always force the heart out of position. As the diaphragmatic fenestrum, through which such a hernia may occur, is usually on the left side, the heart is displaced toward the right; such a malposition is essentially similar to acquired ectopia resulting from diaphragmatic hernia.

3. Pectoral Heart.—The heart may ie anterior to the chest-wall; the wall may be absent, or it may have partly closed behind the misplaced heart; in rare instances there may be no pericardium, and less frequently the heart is extracorporeal,—*i. e.*, outside the body,—the integument having partly united behind it. Such conditions are not compatible with prolonged extrauterine life, and are usually associated with other fissural malformation of the thoracic and abdominal walls.

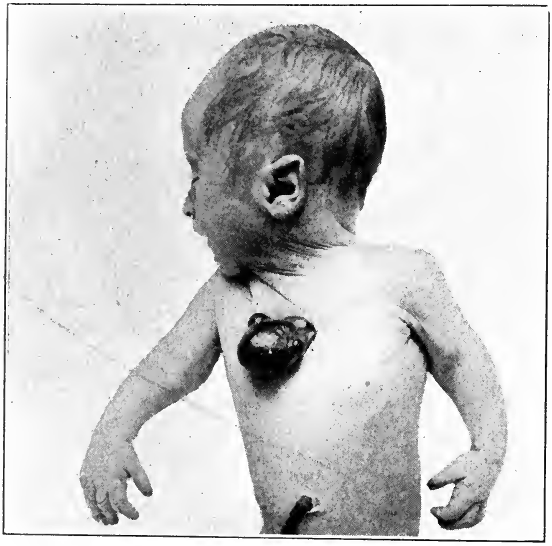


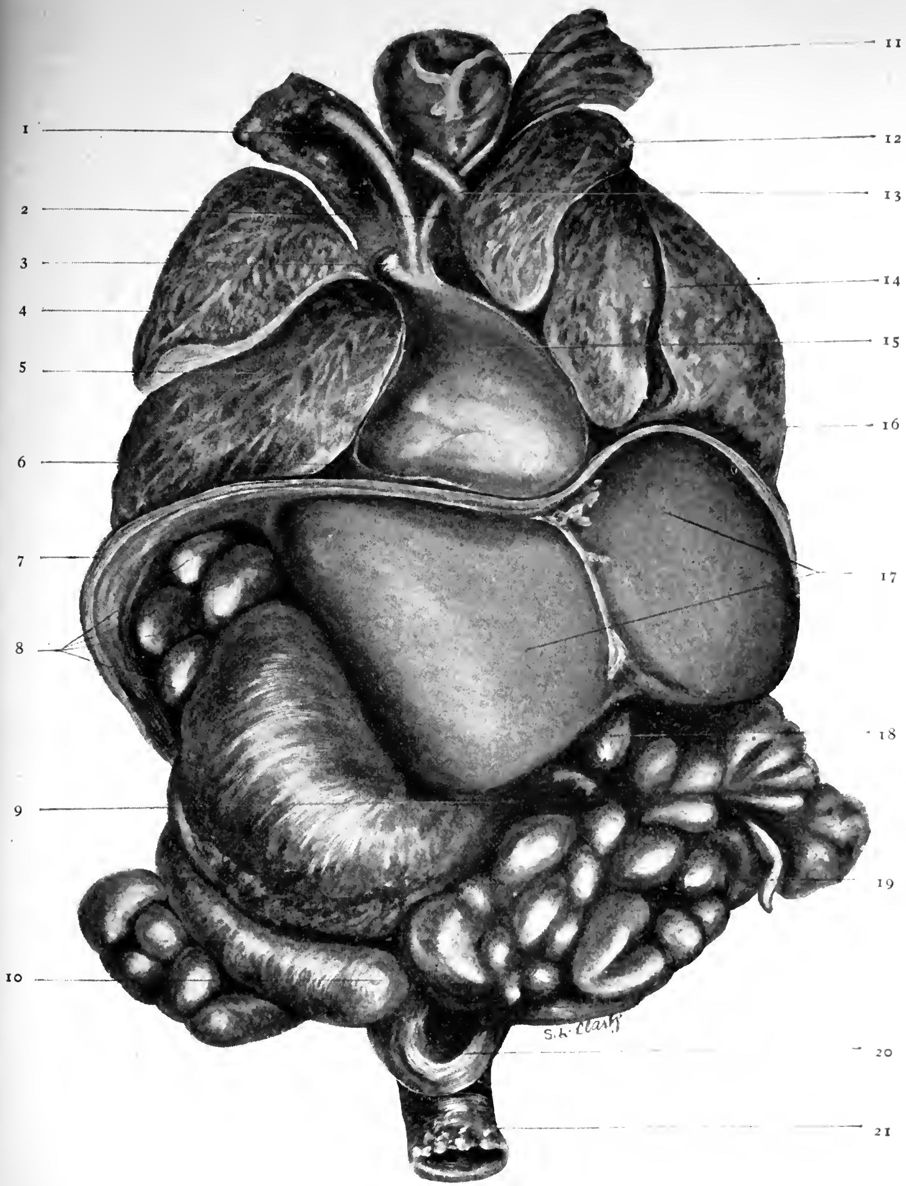
FIG. 242.—PECTORAL HEART.
The chest wall has partly closed behind the misplaced organ, which is connected with the interior of the body by a pedicle composed of the large vessels. The child lived twenty-three and a half hours. (The illustration is from a photograph.)

4. Dexiocardia.—A heart on the right side is compatible with life, and is recognized by insurance companies as not in any way, of necessity, increasing the risk. Vehsemeyer[1] states that but twenty cases of true dexiocardia have been reported. It is usually associated with transposition of the abdominal viscera, the liver going to the left side, etc., the combination of transposed organs being known as the *situs inversus*.[2] This condition is also called transposition, inversion, lateral inversion of the viscera, **hetero-**

[1] "Deut. med. Woch.," March 18, 1897. See also Garnier, "La Presse Méd.," July 12, 1899, p. 15. Magnan, Perpère and Clayeux, "C. R. Soc. de Biol.," tome v, 1903, p. 1460. Baldenweck, "La Tribune Méd.," Aug. 6, 1904. Fraser, "Edinburgh Med. Jour.," Oct., 1904. Le Goic, "Rev. de Méd.," 1904, p. 631. Reichelmann, "Deut. Zeit. f. Chir.," 1904, Bd. 74, p. 354.

[2] Ballantyne, "Scottish Med. and Surg. Jour.," Nov., 1897, p. 1020. Arneill, "Amer. Jour. of Med. Sci.," Nov., 1902, p. 885. Conklin, "Anatomischer Anzeiger," 1903, Bd. xxiii, No. 23. Pritchard, "Soc. for the Study of Diseases in Children," Jan. 15, 1904. Saigol, "Indian Med. Gazette," Nov., 1903. Siewert, "Berl. klin. Woch.," Feb. 8, 1904. Hartland, "Lancet," April 9, 1904, p. 1017. Fraser, "Edinburgh Medico-Chirurg. Soc.," July 6, 1904. Riechelmann, "Münch. med. Woch.," Oct. 25, 1904. Little, "Johns Hopkins Med. Soc.," Nov. 7, 1904, report in "Med. News," 1904. Kitaj, "Med. Soc. of Prague," Nov., 1904. Habermann, "Münch. med. Woch.," July 26, 1905, p. 1348.

PLATE X.



Incomplete Heterotaxy.

(Viscera from case reported by Drs. Royer and Wilson, illustration used by their permission.)

1. Right common carotid.
2. Left common carotid.
3. Arch of aorta.
4. Upper lobe of right lung.
5. Lower lobe of right lung.
6. Pericardium.
7. Diaphragm.
8. Spleens.
9. Pylorus.
10. Sigmoid.
11. Larynx.
12. Upper lobe of left lung.
13. Right innominate vein.
14. Middle lobe of left lung.
15. Heart.
16. Lower lobe of left lung.
17. Liver.
18. Gall-bladder.
19. Appendix.
20. Bladder.
21. Rectum.

taxy, and situs viscerum inversus (Plate X). In typic cases the organs are so arranged that if observed in a mirror they appear in their normal positions and relations. Ballantyne discusses many theories that have been advanced explaining the condition; none is satisfactory. Transposition of all the organs is very much more common than partial heterotaxy. Pic in 1895 collected 190 cases of more or less complete transposition.

Wandering heart, mobile heart, and **cardioptosis**[1] are names applied to cases in which the heart shows unusual degrees of mobility. In such cases changes in posture are attended by conspicuous alterations in the location of the apex of the organ. Barié refers to a case in which the movement amounted to 14 cm. Abrams records an instance in which the patient voluntarily could displace the apex from the fifth to the seventh intercostal space. In many of these cases the condition is congenital, and the proof that it is ever acquired is not conclusive. Rummo thinks that it may be acquired, but is due to congenital abnormal predisposition and results from altered tone in the great vessels by which it is suspended; deficiency in the elasticity of these structures may also be the cause.

Any one of these malpositions may be partial or complete, no two cases being equally marked.

(B) ACQUIRED MALPOSITION.

The heart may be displaced by pressure applied by neighboring or adjacent organs: *e. g.*, by hydrothorax pushing the organ toward the unaffected side; under this head should be included the malpositions due to aneurysm and mediastinal disease.

Emphysema of both sides pushes the heart downward; emphysema affecting one lung displaces the heart to the opposite side. Pleurisy, with contraction, or a contracting fibroid pneumonia, may pull the heart toward the affected side. Vegas and Aguilar[2] record an instance in which dexiocardia was due to hydatid cysts of the left lung and pleura. Diaphragmatic hernia displaces the heart to the right and similar ectopia results from eventration of the diaphragm. The last-named condition is a peculiar malformation of the diaphragm characterized by absence of muscle on one side, permitting the affected area to ascend into the thoracic cavity; the lung on the side involved is collapsed and the heart displaced. The stomach, intestine, and spleen usually occupy the abnormal dome-shaped cavity. In hypertrophied hearts the axes are more nearly parallel with the axis of the body and nearer the median line.

MALFORMATION OF THE HEART.[3]

1. Walls, including the septa:

(*a*) Single cavity.

[1] Barié, "La Presse Méd.," Jan. 27, 1904, p. 57; bibliography.

[2] "Rev. de la Soc. med. argentina," September–October, 1904.

[3] Thorel, "Lubarsch and Ostertag's Ergebnisse d. allg. Path. u. path. Anat.," Neunter Jahrg., I Abt., 1903, p. 585; bibliography. Robinson, "Bulletin of the Ayer Clinical Laboratory of the Penna Hosp.," Jan., 1905, No. 2, p. 45. See also Hektoen, "Amer. Jour. of Med. Sci.," Feb., 1901, vol. cxxi, p. 163. Saillant, "Soc. Méd. des Hôp.," 1905. Garnier, "La Presse Méd.," Dec. 2, 1903, p. 830. Wright and Drake, "Trans. of Assoc. of Amer. Phys.," 1903. Maude E. Abbott, "Osler and McCrae, Modern Med." vol. iv.

(*b*) Arrest of cardiac development with a single auricle and a single ventricle, a condition permanent in the chelonia and scaly reptiles.

(*c*) Single auricle with perforate septum between the ventricles.

(*d*) Single auricle, or a patent foramen ovale, an attempt at closure of the septum between the auricles, with normal ventricles.

2. Blood-vessels.

As in intrauterine life the vessels are developed from five branchial arches, it is possible to have innumerable malformations of the great vascular trunks. The following are most frequent:

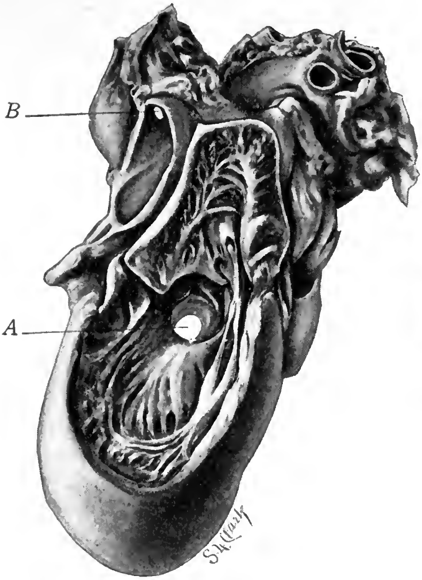


FIG. 243.—MALFORMATION OF THE HEART.
A. Fenestrum in undefended space. *B*. Patulous ductus arteriosus. (Child one year old.)

FIG. 244.—HEART SHOWING ABSENCE OF ANTERIOR PORTION OF AURICULAR SEPTUM.

(Drawing is two-thirds the natural size.)

The anterior portion of the septum is lacking, the remainder being largely membranous in structure. The oval light area below and slightly to the right of the opening probably corresponds to the foramen ovale, although this may be included in the opening. The patient had no cardiac symptoms and during her fatal illness (pneumonia) there was, at no time, a suspicion of cardiac abnormality. Age thirty-two years.

(*a*) *Patent septum* between the pulmonary artery and aorta, a condition permanent in the crocodile. The fact that the aorta and pulmonary artery develop from a single trunk renders the condition possible.

(*b*) *Transposition of the vascular trunks*, the pulmonary artery arising from the left heart and the aorta from the right. In some cases the transposition of the vascular trunks is also associated with transposition of the ventricles, constituting what Rokitansky called *corrected transposition*.

Fig. 1.
Malformed Heart.

a. Aorta. *b*. Pulmonarv orifice. *c*. Opening through ventricular septum. *d*. Right auricular ventricular orifice. *e e*. Rudimentary left ventricle. *f*. Interventricular branch of left coronary artery

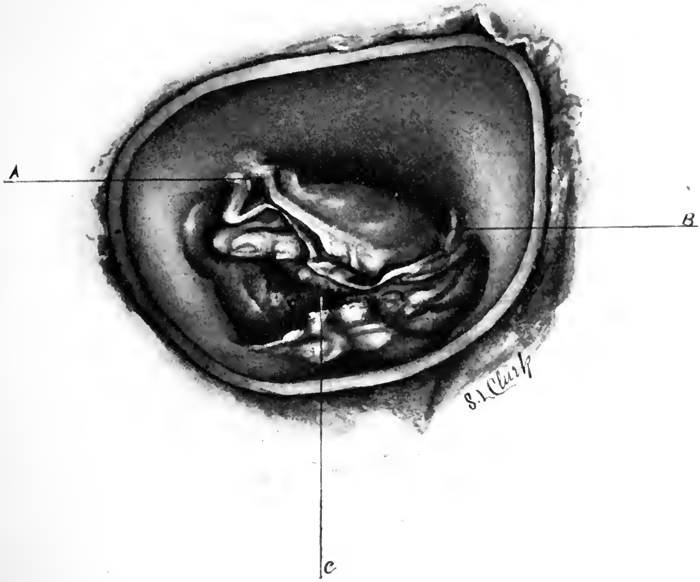


Fig. 2.
Aortic Stenosis Seen from Aorta.

Chronic Endocarditis with fusion of two leaflets, converting aortic orifice into slit-like opening extending from *A* to *B*. *C*. Point of fusion between the two leaflets. All leaflets are greatly thickened and the sinuses of Valsalva are partly occupied by newly formed tissue.

(*c*) *Double Aorta.*—In development there are two primitive aortas, a right and a left; ordinarily the right disappears, but it may not do so.

(*d*) *Patulous Ductus Arteriosus.*—When a stenosis of the pulmonary artery develops before occlusion of the ductus arteriosus, the communication between the aorta and pulmonary artery may remain permanent. There is little difference between this and *a*, except the location, the latter being immediately at the heart.

(*e*) *Stenosis of the pulmonary artery* is probably the most frequent cardiac abnormality, excepting, of course, patulous foramen ovale. The degree of stenosis varies, and may be situated immediately at the valvular orifice or slightly beyond this point, or may be manifest in the trunk some distance from the orifice. Occasionally, stenosis affects the *conus arteriosus*. Stenosis may involve the aorta.

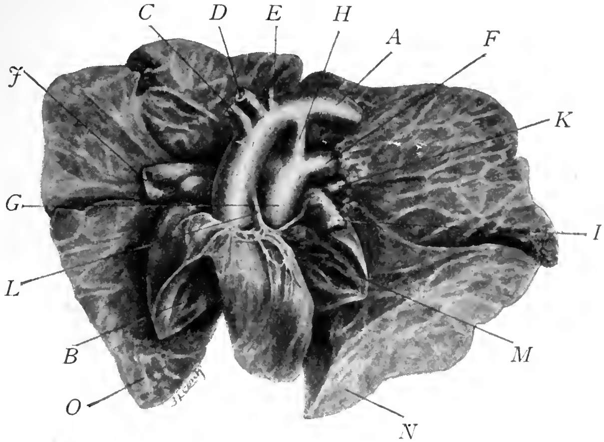


FIG. 245.—HEART, GREAT VESSELS, AND LUNGS FROM A CASE OF TRANSPOSITION OF THE VASCULAR TRUNKS. Child lived thirty-four days. Autopsy by Dr. Ellis. Philadelphia Hospital Specimen.

A. Aorta which arises from the right ventricle. *B*. Right ventricle laid open. *C*. Innominate. *D*. Common carotid. *E*. Subclavian. *F*. Left branch of the pulmonary artery; the right branch can be seen passing under the aorta, and from the point where the right and left pulmonary arteries are given off by the main trunk (*G*) the ductus arteriosus (*H*) arises and passes upwards to the aorta (*A*). *I*. Left auricle. *J*. Right auricle. *K*. Left pulmonary vein. *L*. Left coronary artery which arises 0.7 cm. above the origin of the abnormally placed aorta. *M*. Left ventricle. Notice that the right ventricular wall is the thicker of the two. *N*. Left lung. *O*. Right lung.

(*f*) *Atresia* of the pulmonary artery or of the aorta is possible only with persistent communication between the two vessels beyond the point of occlusion.

3. Valves.—These being developed from the endocardium, may be in excess as to number of leaflets, or the reverse; a leaflet may be redundant or deficient. Care must be taken not to confuse the results of antenatal endocardial disease with malformations.

Hypoplasia of the heart is occasionally observed. The organ is small,—may be less than one-half the normal size and weight,—and usually possesses proportionately small vessels. The vessels may be hypoplastic without the heart showing marked abnormality. The organ may be absent.

Causes.—Malformation of the heart is dependent upon arrest or perversion of development. The stage in its evolution at which this

occurs largely determines the character of the malformation. When cardiac development is arrested early, the organ manifests the widest deviations from the normal. When it is delayed until later in intra-uterine life, or when the usual circulatory changes at birth fail to take their normal course, malformation is usually not marked, and commonly gives rise to no phenomena leading to a suspicion of its presence later in life.

Aside from arrest of development, as a cause of cardiac malformation, there can be no doubt that antenatal endocarditis may give rise to changes in the valve leaflets or in the orifices closely allied to those seen as a result of postnatal endocardial inflammation.

Course and Termination.—Aside from those malformations which mechanically preclude the possibility of postnatal circulation, almost no cardiac deformity has been described that may be not compatible with a more or less prolonged extrauterine existence. The accompanying lesions and associated phenomena are due to circulatory inefficiency, as manifested by tendency toward stagnation and the occurrence of faulty aeration. The mere mixing of arterial and venous blood may produce no symptoms or alterations in other organs or tissues. If the blood can be kept circulating with sufficient activity to secure aeration and to prevent venous distention, the patient may escape any manifestation of the condition. The clubbing of the digits, cyanosis (**morbus cœruleus**), thick lips, and stubby nose with thickened alæ, may all be taken as evidences of disturbed nutrition. The polycythemia may be truly remarkable, as in the case reported by Baunholtzer: pulmonary stenosis was present, and the blood examination showed 9,447,000 erythrocytes and 160 per cent. hemoglobin. The relatively high specific gravity of the blood of the new-born (1060 to 1070) often persists. Holt collected 242 cases of malformation of the heart, in 4 of which there was an associated acute endocarditis. Robinson[1] has been able to collate 17 cases of acute endocarditis complicating congenital malformations; he adds two original observations.

General atrophy of the heart occurs as the result of general wasting, with or without lessened work, the organ being very much decreased in size and weight. A specimen in the writer's laboratory weighs less than three ounces. The condition can usually be differentiated from hypoplasia by the fact that the blood-vessels remain approximately normal in size, while the corrugations of the pericardium and endocardium indicate the diminution in volume.

Local atrophy of the heart affects the left ventricle, and is probably a sequence of disuse. A stenotic mitral orifice permits but little blood to flow into the left ventricle and gives it but little work. The nutrition is also in most cases below the normal. The condition is usually accompanied by an unusual dilatation of the right side, which may also be hypertrophied. Wasting of the left ventricular wall, under the foregoing circumstances, is comparable to the hypoplasia observed in the left ventricle as a result of atresia of the aorta, or of the right ventricle when the pulmonary artery is similarly affected, in both cases the auricular septum being patulous or absent.

Brown atrophy of the heart is due to persistent congestion of the

[1] "Bulletin of the Ayer Clinical Laboratory of the Penna. Hospital," Jan., 1905, No. 2, p 45.

muscle, and is associated with old age, inanition, and allied conditions. The organ is of a dark chocolate or maroon color, hard and tough, diminished in size and weight, with tortuous vessels and wrinkled endocardium, due to diminution in surface. Hematoidin or hemofuscin is deposited in the muscle-cell as a granular pigment, near the ends of the nucleus (polar pigmentation); the fiber is shrunken, and there is also, probably, a numeric decrease. The exact relation of this pigmentation to wasting of the muscle-fibers is not known. McCallum[1] states that Schiefferdecker regarded polar pigmentation as normal in the heart of individuals after the tenth year. According to Gutch,[2] there is a notable reduction in the weight of the organ before diminution in the size of the fibers becomes demonstrable. The muscle-fibers may waste to the point of disappearance. The fibrous tissue may be notably increased, and occasionally distinct areas of induration may be observed. (See Chronic Myocarditis.)

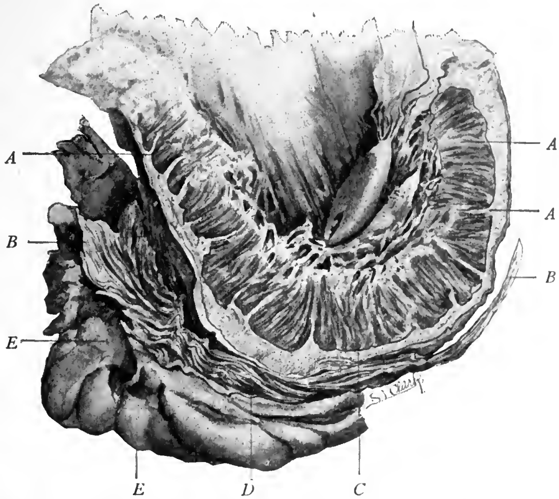


FIG. 246.—FATTY INFILTRATION OF THE HEART AND PARTIAL PERICARDIAL ADHESION.
A, A, A. Columns of fat projecting into the myocardium. *B, B.* Parietal pericardium which is adherent to the apex of the heart from *C* to *D*. *E, E.* Extrapericardial fat.

Fatty infiltration of the heart occurs in general obesity; after the permanent changes incident to pericarditis; in chronic alcoholism; occasionally, in the aged and the insane. There is enormous increase in the subpericardial fat; fat-cells infiltrate between the muscle-fibers, and probably incommode their action. Often the fat hangs as polypoid masses from the apex of the organ or along the groove of the ventricular septum. From the margins of the auricles tuberous masses of fat, sometimes 2 cm. in thickness, hang like pendulous new growths. Some believe that atrophy of the fiber may be induced; during the early stage of the process this is not probable, as the fibers in the mass

[1] Anatomischer Anzeiger, "Centralbl. f. die gesamte wissenschaftliche Anatomie," 1897, Bd. xiii, No. 23.
[2] "Jour. of Path. and Bact.," June, 1901.

are, usually, histologically normal. The condition is sometimes spoken of as *lipomatosis of the heart.* It should not be forgotten that this condition constitutes a most frequent cause of sudden death, the over-crowded muscle-fibers failing to contract, or the fat, having penetrated between the muscle-fibers, weakened the interlacing network and led to rupture. The columns of fat may extend through the cardiac wall. A marked overgrowth of the fat, and persistence of the causes that lead to its accumulation, not infrequently terminate in an associated degenerative change in the muscle-fibers. Recently there has been a tendency to consider fatty infiltration and fatty degeneration as identical processes. While freely admitting considerable doubt as to the exact nature of the change in each case, none could consider identical the changes represented by Fig. 133, page 226, and Fig. 142, page 244. In some cases of lipomatosis the muscle-fiber, even where the fat is intercalated, is normal in color and texture, and often is firm at autopsy. This condition is clearly distinct from the soft, flabby organ, the muscle of which looks like washed meat, and, when subjected to the proper reagents, the fibers are found to contain a substance indistinguishable from fat; in most of the latter group of cases there is no increase in the subpericardial fat nor are columns of adipose tissue intercalated between the muscle-fibers.

Lardaceous Disease.—*Albuminoid or amyloid infiltration of the heart* may occur in the blood-vessels of the organ and in the myocardium. The heart is undernourished and anemic; milky opacity of the endocardium of the right auricle is the most common macroscopic phenomenon, although any of the cavities may exhibit the change. It responds to the usual stains, but can rarely be detected except by the microscope. As a rule, the alterations in the muscle-fiber are inconspicuous, the amyloid deposit being restricted to the blood-vessels and the connective tissue between the fibers. Sometimes the deposit of lardacein is nodular rather than diffuse. Such a case was reported by Steinhaus;[1] the amyloid and hyaline nodules were irregularly distributed in the myocardium.

Calcareous infiltration of the heart may occur around the auriculo-ventricular orifice, usually of the left side, in the valves, in the heart muscle, and under the pericardium. If any of these structures have been inflamed, infiltration of the inflammatory products with lime salts is likely to ensue. Deposit of lime salts is not infrequent in areas of myocardial sclerosis and in old infarcts and other necrotic areas. It is also a common occurrence in connection with tuberculous and syphilitic lesions of the myocardium. In some instances the extent of the calcareous infiltration was beyond anything that could have been anticipated. In the case reported by Bramwell[2] the ventricular wall, muscle columns, and even the papillary muscles were affected. Many similar[3] but probably less marked cases have been recorded. In Dufour's patient the deposit was nodular. An interesting observation in connection with these cases is the slowness of the pulse, which sometimes ranges between 30 and 40.

[1] "Zeit. f. klin. Med.," vol. 45, Nos. 5 and 6.
[2] "Edinburgh Hospital Reports," vol. iv, p. 175.
[3] Pessel, "Münch. med. Woch.," June 10, 1902. Fowler, "Brit. Med. Jour.," April 23, 1904, p. 952. Dufour, "La Bulle. Méd.," June 11, 1904.

Pigmentary Infiltration of the Heart.—By some, brown atrophy is considered as a form of infiltration and is described under this title. (See p. 488.)

Granular degeneration of the heart, or **cloudy swelling,** is probably an initial stage in a form of fatty degeneration. (See Fig. 139, p. 242.) It occurs in infectious processes, such as septicemia, erysipelas, diphtheria, beri-beri, scarlet fever, and typhoid fever; in hyperpyrexia, as that of thermic fever; and in exhausting diseases generally, such as pernicious anemia. The influence of bacterial toxins in the production of the process can not be doubted. It may be associated with pericarditis or endocarditis, either as a result of the inflammation or dependent upon the same cause. The heart muscle is softer than normal, is slightly edematous to the touch, and is grayish and cloudy, in striking contrast to the bright red of the normal. Rigor mortis is absent in advanced cases. The muscle-cells are more or less loaded with granular debris, albuminoid and not fatty, at this stage, as is shown by the granules clearing up when treated with acetic acid, and not being soluble in alcohol or ether.

Fatty degeneration of the heart occurs: (1) As a general process invading the entire organ or the whole of one ventricle; (2) secondary to some local lesion, and restricted to a small area; (3) due to poisons, as phosphorus.

1. Diffuse or General Fatty Degeneration of the Heart.[1]—This form arises from the same causes as, and is probably merely a later stage of, granular degeneration. It is frequently associated with arsenic, phosphorus, chloroform, and alcohol poisonings, and other toxic conditions. More or less fatty degeneration of the heart is observed in gout, diabetes, and chronic parenchymatous nephritis, particularly when uremia is present. A varying quantity of fatty degeneration will be found in the wasted hearts of chronic pulmonary tuberculosis. The papillary muscles and columnæ carneæ of the left ventricle show the change to the best advantage; they are light brown in color, and running across them are yellow striæ, giving them a brindled, streaked, or flecked appearance—"tabby-cat" or "tiger-heart"; in some instances the muscle is pale yellow rather than brown, at other times brownish-yellow—the "faded-leaf" color, or "thrush breast" appearance; in the cut wall the fiber lines just below the pericardium are lost, and the tissue appears, as a rule, uniformly yellow. Looking through the pericardium, or, better, the endocardium, the muscle shows yellow and red striæ, the latter being the unaffected fibers. The process is diffuse but not universal, comparatively normal fibers lying next to more or less altered ones. The cardiac wall may be thinned as a result of dilatation, and the orifices may be dilated. The specific gravity of the muscle is lessened. The myocardium can usually be readily pinched through. Microscopic or even macroscopic hemorrhages into the heart-wall may be present. Under the microscope the affected fibers are loaded with minute oil globules not larger than a red corpuscle. They

[1] Satterthwaite, "Med. News," Feb. 2, 1901. Robinson, "Phila. Med. Jour.," May 11, 1901, also "Amer. Jour. of Med. Sci.," June, 1901. Pratt, "Johns Hopkins Hosp. Bull.," Oct., 1904. Bolton, "Lancet," Feb. 4, 1905, p. 278. Cowan, "Jour. of Path. and Bact.," June, 1902, vol. viii, p. 177. Thorel, "Lubarsch and Ostertag's Ergebnisse d. allgem. Path. u. path. Anat.," Neunter Jahr. I. Abt. 1903, p. 612.

differ from granular fibers in that the fat is darkened by osmic acid and may be dissolved in ether. (See Demonstration of Fat, p. 244.) Dunham[1] believes that the notable swelling present in the fibers, during the earlier stages of the process, may be due to the fact that the fiber takes up nutritional substances that it can not properly convert; this belief is in line with the conviction of other observers that the process partakes of some of the characters of an infiltration. According to Cowan, the cement substance between the cells and the nuclei never becomes fatty. In some cases fat droplets can be demonstrated in the capillary endothelium, and in such instances the myocardial change is usually most marked immediately around the affected vessels (para-arterial or peri-arterial form).

The termination of the granular and fatty metamorphoses is likely to be the same: (*a*) sudden syncope and death from failure to contract; (*b*) gradual failure by reason of increasing incompetency to maintain the circulation. Rupture of the heart is not common in diffuse or general fatty degeneration of the organ, as the cardiac muscle has not the power so to raise the intracardiac pressure as to endanger the weakened walls. It is probable that, in the granular stage, regeneration and recovery may ensue; this becomes less likely as the fatty stage advances. Clinicians commonly maintain that repair is possible even when fatty change is advanced. Under such circumstances it is held that the destroyed fiber is absorbed and the adjacent fibers undergo hypertrophy, and in that way compensate for the tissue that has been lost. As it is not improbable that in cardiac hypertrophy new fibers are formed, with the associated enlargement of existing fibers, the possibility of a similar change following the subsidence of the disorder at present under consideration must be admitted.

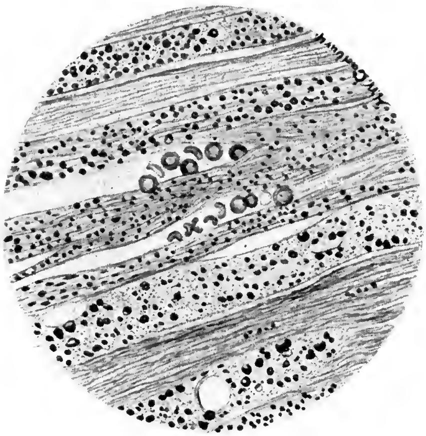


FIG. 247.—FATTY DEGENERATION OF THE HEART. (Specimen fixed in osmic acid, rendering the fat globules black.)

Near the center of the drawing are a number of red blood-cells. (*From a case of pernicious anemia in the Jefferson Medical College Hospital, service of Professor J. C. Wilson.*)

2. The second form of fatty degeneration is sometimes spoken of as partial or *local*. It is due to a local ischemia, such as results from atheroma, calcification, embolic plugging, or thrombosis of some branch of the coronary arteries, which are, to a certain extent, terminal. The lesion is manifested by the presence of a softened spot in the ventricular wall, pale yellowish-brown in color, frequently greasy to the touch, and occasionally containing oil globules, visible macroscopically. Sometimes the degenerated area is surrounded by a zone of hyperemia. The rapidity with which the process develops varies in different cases, depending upon the promptness with which the cause acts. When there

[1] "Med. Record," Feb. 16, 1901.

has been a sudden occlusion of the blood-supply, the process will commonly be rapid. On the other hand, when the local change is brought about by gradual encroachment upon the lumen of the coronary artery or a branch, the lesion is delayed, and opportunities are afforded for an associated overgrowth of fibrous tissue. As a rule, the degenerative change is limited to a single focus, which is located on the anterior aspect of the left ventricle near the apex. Less commonly, a corresponding point on the wall of the right ventricle is involved. The degenerated area is rarely large, as the conditions that bring it about, if affecting a considerable extent of the cardiac wall, usually cause death before the manifestation of any degenerative lesion. Occasionally, more than one area is involved. Microscopically, the changes already described are more marked than in the general variety, as the patient usually lives longer, and the small focus advances further. The process may be followed by: (*a*) Rupture, which is rare in the general degeneration; (*b*) aneurysmal bulging; (*c*) fibroid processes may convert the mass into cicatricial tissue; (*d*) the area may be so small as to give no determining phenomena. (See Infarction of the Coronary Arteries.)

3. The third form of fatty degeneration,—that due to poisoning,—*toxic degeneration of the heart muscle*, results most commonly from phosphorus, but occasionally from arsenic and antimony. It presents the changes already given, and responds to the general stain and chemic tests of the ordinary fatty degeneration; if an opinion is to be given in a suspected poisoning case as to the presence or absence of fatty degeneration, it must be formed, if it is possible to form such an opinion, while the tissue is fresh. The term *toxic degeneration* is not altogether appropriate, as the degenerative changes resulting from various infections are essentially of toxic origin.

Hyaline degeneration of the heart differs from the albuminoid or granular change in that the heart muscle-fibers are converted into a hyaline, vitreous substance resembling the material that results from the vitreous change in other muscles, known as Zenker's degeneration. When present, the structural alteration has been discovered by the microscope and not by macroscopic evidences. In hyaline degeneration the muscle-fibers may be fragmented; the separation of the fragments may be at the junction of the muscle-cells or directly through the cell-wall. When this condition is present, Renaut has proposed the name **segmentary myocarditis,** or **myocardial segmentation** or **fragmentation.**[1] Bulig is of the opinion that many, if not all, instances of segmentation and fragmentation are artifacts produced by the microtome knife. Strekeisen believes that the fragmentation is dependent upon violent cardiac contractions during the agonal period. He holds that a preliminary weakening of the muscles is not necessary to the occurrence of fragmentation, as shown by the frequency with which it occurs when death has been due to accident and when no associated lesions can be detected.

Postmortem Changes in the Myocardium.—Peculiar patches of a yellowish or grayish-yellow color, situated immediately under the pericar-

[1] Thorel, "Lubarsch and Ostertag's Ergebnisse d. allgem. Path. u. path. Anat.," Neunter Jahr. I. Abt. 1903, p. 622. Buhlig, "Jour. Med. Research," May, 1902. MacCallum, "Anatomischer Anzeiger," 1897, xiii, p. 609. Giacomelli, "Rif. Med.," Nov. 3, 4, and 5, 1902.

dium, have been noticed. They usually contain bacteria, but not the tissue reactions incident to an infection. The change resembles, in a limited way, an embolic process. Weber regards the condition as a postmortem change in an area of infection, which infection occurred just before death.

Myocarditis, or inflammation of the cardiac muscle, may be acute or chronic, local or diffuse, and, though primary types have been described, it is probably always secondary to some other affection. With regard to the genesis of the condition, one of the first difficulties encountered is differentiation of inflammation from some of the degenerative changes described in previous pages. The scope of this work does not permit a discussion of the clinical and pathologic phases of the subject. It may be stated, however, that clinicians and pathologists are not agreed as to the line that may be drawn between myocardial degenerations, necrosis, and inflammations. There are points at which the three conditions appear to become indistinguishable. For the purpose of this work acute myocarditis may be divided into the simple and suppurative, and the chronic myocarditis into the fibroid, and fibroelastic or elastic types.

The term **acute parenchymatous myocarditis** has been applied to the lesions that I have characterized above as degenerative. Theoretically in this form the alteration is restricted to the muscle-fiber with no important alteration and no cellular infiltration in the interstitial tissue. The condition possesses no anatomic feature or clinical character by which it may be separated from some of the myocardial degenerations. For these reasons my inclination is to suppress the term.

Acute nonsuppurative or **simple myocarditis**[1] is observed in acute infectious diseases, particularly those due to organisms incapable of producing suppuration. The condition is observed in rheumatism, diphtheria, influenza, chronic uremia, smallpox, and occasionally in pneumonia, typhoid, malaria, and syphilis. The essential feature in its production seems to be intense toxemia, and apparently the condition may occur without the presence of bacteria in the myocardium. In cases reported by Sellentin bacteria were not found in the affected myocardium nor was there evidence of infection in other tissues. According to Escudero, the myocarditis of influenza may be of the acute, nonsuppurative type, in which case it is toxic, or mixed infection may give rise to the suppurative lesion. It has been observed in tuberculosis even when there was no evidence of the tubercle bacillus in the myocardial structures.

[1] The following references on acute myocarditis may be consulted: Thorel, "Lubarsch and Ostertag's Ergebnisse d. allgem. Path. u. path. Anat.," Neunter Jahr. I. Abt. 1903, 632. Hektoen, "Jour. of Path. and Bact.," Jan., 1896. Freund, "Berl. klin. Woch.," Dec. 5 and 12, 1898. Gibson, "The Practitioner," Jan., 1901. Bianchini, "Riv. di patol. nerv. é ment.," 1901, No. 9. Aubertin and Babonneix, "Gaz. des Hôp.," Aug. 8, 1901. Merklen, "La Presse Méd.," Dec. 4, 1901. Stengel, "Jour. Amer. Med. Assoc.," Dec. 14, 1901. Fisher, "Brit. Med. Jour.," Sept. 27, 1902, p. 949. Cowan, "Jour. of Path. and Bact.," Aug., 1903, p. 87. Guido, "Brit. Jour. of Child. Dis.," vol. i, No. 12. Sotti, "Arch. per le Sc. med.," 1904, vol. xxviii; also "Giornale della R. Accad. di Med. di Torino," February–March, 1904. Carpenter, "Lancet," Oct. 1, 1904, p. 947. Schmaltz, "Münch. med. Woch.," Aug. 9, 1904. White and Smith, "Boston Med. and Surg. Jour.," Oct. 20, 1904. Sellentin, "Zeit. f. klin. Med.," 1904, Bd. liv, p. 208. Escudero, "Argentina Med.," Nov. 19, 1904.

Morbid Anatomy.—The heart is usually softer than normal and, as a rule, pale. In some cases, however, the color is dark and beefy, but rarely uniformly so. When local or nodular, pale grayish areas indifferently outlined may sometimes be recognized. Histologically the muscle-fibers are swollen, the nuclei obscured, and the interstitial tissue of the affected area contains mononuclear cells, some of which may possess the morphology and stain reaction of plasma cells. In advanced cases areas can be found in which the muscle-fibers have disappeared, the space so created being occupied by mononuclear cells. The percentage of these cases in which recovery occurs is not known, nor are we in possession of any accurate information as to the later changes in patients who survive. It has been held that the acute, nonsuppurative, interstitial myocarditis may constitute the basis of a chronic fibroid lesion that develops later. There can be no doubt that the cardiac symptoms, in many acute infectious diseases, may be due, at least in part, to acute, nonsuppurative myocardial inflammation.

Acute suppurative myocarditis—*myocardial abscess* or *metastatic abscess of the heart*—usually follows an infection of the cardiac wall induced by the deposit of infected emboli. The condition is most frequent in pyemia and septicemia, and particularly in such mycoses of the blood as commonly accompany osteomyelitis, suppurative thrombophlebitis, and endocarditis due to pyogenic organisms. In other cases the infection results from extension of bacteria from the endocardium or pericardium. The foci of suppuration are usually situated in the anterior portion of the left ventricular wall. In the earlier stages they present the gross appearances of an infarct; later, pus may be evident, and may burrow toward the endocardium or the pericardium. The abscesses are rarely large, are not infrequently microscopic, but may attain a diameter of 0.25 to 0.5 cm. The adjacent heart muscle usually shows the changes incident to infective processes independent of actual bacterial invasion.

Chronic interstitial or sclerotic myocarditis[1] (also called productive myocarditis, fibrous transformation, fibrous degeneration of the myocardium, and fibrous infiltration) is a chronic process associated with the formation of fibrous tissue in the myocardium.

Causes.—Although not established beyond the possibility of a doubt, it is probable that acute nonsuppurative interstitial myocarditis may lead to the chronic fibroid form. The most frequent cause of myocardial induration is disease of the coronary artery of such a type as to lessen the blood-supply in the main trunk or in one or more of its branches. This influence may result from atheroma of the aorta so situated as to involve the coronary artery at its point of egress; a nodular ring often surrounds the coronary in such a way as clearly to lessen the

[1] Thorel, "Lubarsch and Ostertag's Ergebnisse d. allgem. Path. u. path. Anat.," Neunter Jahr. I. Abt. 1903, p. 645. Fujinami, "Virchow's Arch.," 1900, Bd. 159, p. 447. Musser, "Medical News," Jan. 11, 1902, also April 19, 1902. Cowan, "Jour. of Path. and Bact.," Dec., 1903, p. 210. Gibson, "Lancet," Dec. 5, 1903, p. 1565. Jackson, "Boston Med. and Surg. Jour.," Sept. 29, 1904. Aschoff, "Arch. de Med. Exper. et d'Anat. Path.," Nov., 1904, p. 984. Marchiafava, "Revista Crit. di Clin. Med.," April 23, 1904. Zuppinger, "Arch. f. Kinderheilkunde," vol. xxxv. Camac, "Johns Hopkins Hosp. Bull.," Feb., 1904, vol. xv. Coplin, "Proceed. of Path. Soc. of Phila.," n. s., vol. vi. Mouriquaud, "Soc. des Sci. Méd. de Lyon," Feb. 1, 1905.

lumen and reduce the quantity of blood that enters the vessel. In other cases the sclerotic process affects one or more of the coronary branches, producing a local effect on nutrition and terminating in the evolution of a more or less circumscribed area of so-called fibroid myocarditis. The branch usually affected is the anterior interventricular stem, usually in the lower third of the course. In the heart from which the diagram shown in Fig. 248 was made the periventricular branch was affected, and at this point a notable increase in fibrous tissue and a proportionate wasting of the muscle occurred, giving rise to slight aneurysmal bulging.

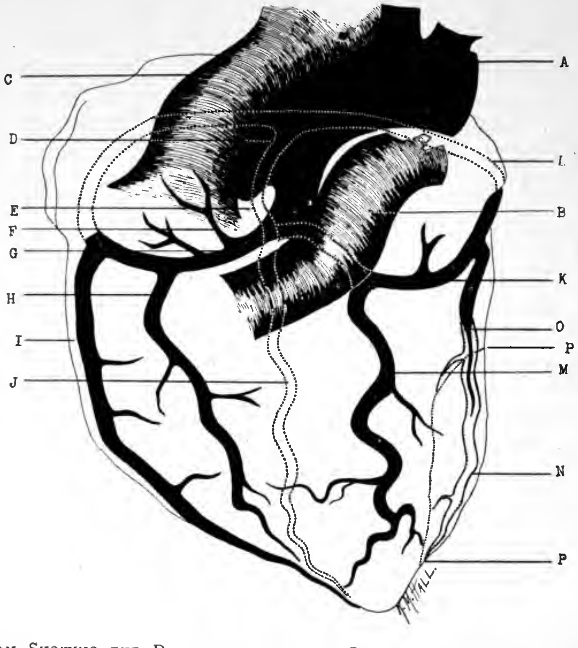


Fig. 248.—Diagram Showing the Distribution of the Coronary Artery in a Case of Local Fibroid Myocarditis.

A. Aorta. *B*. Pulmonary artery. *C*. Superior vena cava. *D*. Posterior interventricular branch of the right coronary artery. *E*. Auricular appendage. *F*. Right auricular branch. *G*. Right coronary artery. *H*. Periventricular branch. *I*. Right marginal branch. *J*. Posterior interventricular branch of the right coronary artery. *K*. Left coronary artery. *L*. Terminal branch of the left coronary artery. *M*. Anterior interventricular branch of the left coronary artery. *N*. Occluded artery corresponding in position to the left periventricular branch. The left marginal branch was farther to the side and could not be indicated in this drawing without causing confusion. *O*. Point of occlusion. *P*, *P*. The dotted line marks the border of the most advanced myosclerotic area.

So constantly is fibroid myocarditis associated with disease of the nutrient vessels that Musser has suggested calling the condition coronary artery disease. It may also accompany chronic endocarditis, either associated with, or independent of, valvular incompetency or stenosis. Chronic inflammations of the pericardium, congestion of the cardiac veins, increased venous tension, such as is seen in emphysema, interstitial pneumonia, and chronic pleurisy, are also causes. It is a more or less constant lesion in failing compensation, and constitutes one of the manifestations of syphilis and of malaria. It is maintained that the sclerotic

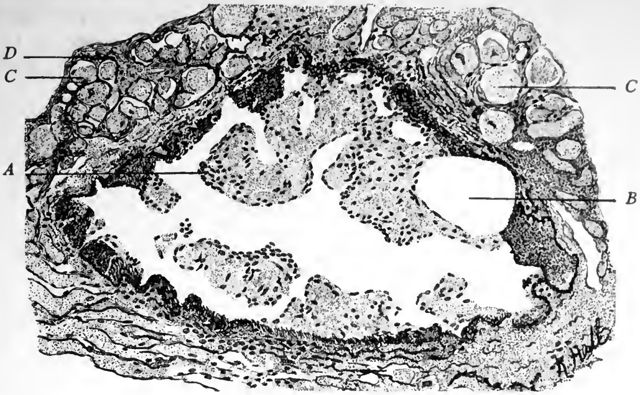


FIG. 249.—ARTERIOSCLEROTIC DISEASE OF THE CORONARY ARTERY GIVING RISE TO PROGRESSIVE OBLITERATION OF ITS LUMEN.

Section taken from sclerotic periventricular branch shown in Fig. 248. The elastic lamellæ are fragmented, the endothelium has proliferated, and a forming thrombus is rapidly occluding the vessel.

A. Forming thrombus covered at most points by endothelium. *B*. Channel through thrombus with partial wasting of adjacent vessel wall. *C*, *C*. Transverse section of muscle-fibers, showing fragmentation and retraction from the myocardial skeleton. *D*. Unusually conspicuous, apparently swollen elastica; the same change can be seen in many parts of the field. The fine stipple effect in the lower part of the figure, and especially marked in the lower right, is due to transverse sectioning of elastic fibers.

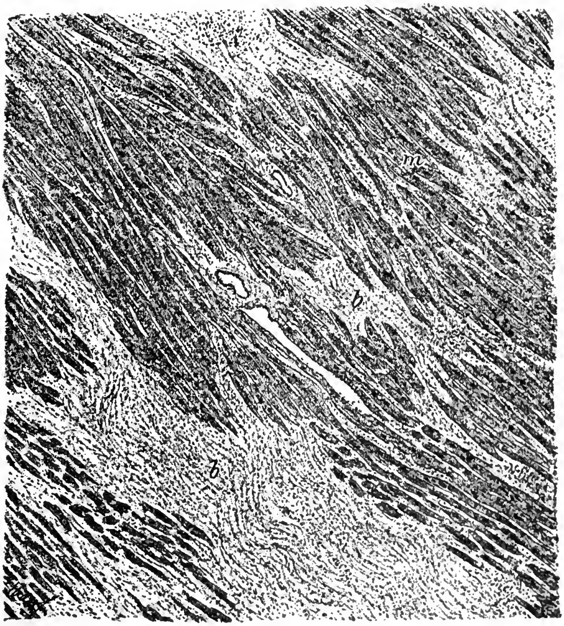


FIG. 250.—CHRONIC MYOCARDITIS.—(*Schmaus.*) × 150 diameters.

m. Cardiac muscle-fibers. *b b*. Newly formed fibrous connective tissue. This can often be demonstrated to be of different ages, and in the older parts calcareous change may have occurred.

changes of myocarditis may be consecutive to myocardial degeneration and necrobiosis brought about by various bacterial toxins. The fibrous increase has been experimentally produced by pyocyaneus-toxin (Charrin), and the poison of the diphtheria bacillus is believed to lead to lesions of the muscle-fibers followed by fibroid increase (Mollard and Regaud). It is generally conceded that the fibrosis is secondary to alterations in the muscle-fiber and not the reverse. The statement that it may result from rupture of the muscle-fibers is not accompanied by satisfactory proof.

Morbid Anatomy.—The preceding review of the important causes of fibroid myocarditis suggests the recognition of two forms. In one of these the process is more or less sharply outlined, and constitutes what may be called the local or circumscribed form of the affection. In other cases the process is diffuse, a large part of the myocardium is affected, although the change is not uniform. To this condition has been given the name diffuse interstitial myocarditis. Weber and also Huchard have proposed certain subdivisions based upon the histology of the affected tissues. It is possible to recognize a perivascular type in which the fibrous tissue immediately surrounds the blood-vessels distributed in the myocardium. In other cases the sclerosis appears to bear no relation to branches of the coronary artery, and for this the name *dystrophic fibrosis* has been proposed. Letulle was the first to call attention to the fact that in some of these cases the new tissue is largely elastica, and for this condition he proposed the name *elastic myosclerosis*. Like the simple fibroid types, this form may be diffuse or circumscribed. In some cases of myosclerosis the involved areas are extremely hard, and for such the name *myosclerosis dure* has been suggested; when the affected areas are soft, the condition is called *myosclerosis molle*.

Local or **circumscribed fibrous myocarditis** is usually attributed to a cause that has affected only a part of the cardiac wall, such as the anemia following gradual occlusion of a branch of the coronary artery, infarction, and local fatty degeneration. The fibrous area may be small, irregularly outlined, and less than one centimeter in diameter. It may or may not extend through the heart-wall. In other cases the area of fibrosis may equal one-third of the ventricular wall, and in some instances larger areas have been found. The process is most frequent at or near the apex of the left ventricle. When fully developed, the fibrous area is dense, like a cicatrix, constituting the so-called "heart-scar." Some of the collections of fibrous tissue probably represent efforts at repair in areas of past necrosis. The fibrous tissue sometimes contains pigment and calcareous matter, and muscle-fibers may be absent. The presence of pigment is suggestive of hemorrhagic infarction. When the entire thickness of the heart-wall is involved, and even sometimes when only a part has become fibroid, aneurysmal bulging may occur. The rather sharply outlined margin, at times observed, suggests that some of these heart-scars are really more or less fully healed gummata. The occurrence of scars of evidently different ages, associated with the presence of absorbing gummata, would certainly seem to be conclusive.

In the **diffuse interstitial myocarditis** the fibrous tissue is widely, but not uniformly, distributed. The abundance of the new tissue between the cardiac muscle-fibers has to a certain extent justified the appellation fibroid infiltration. Most observers, as already stated, do not

consider the increase of fibrous tissue an evidence of past or existing inflammation, but rather a substitutive fibrosis, the fibrous tissue having replaced atrophied, degenerated, or necrotic muscle-fibers.

Morbid Anatomy.—The cardiac muscle is usually firmer than normal; this abnormal density is not uniform in distribution. Occasionally, whitish areas of sclerosis may be recognized in the ventricular wall. White lines are frequently present on the columnæ carneæ; the tendons of the papillary muscles seem to be projected toward the cardiac wall as whitish streaks, often extending nearly to the base of the papillæ. Under the microscope, fibrous tissue can often be demonstrated in various stages of development. Not infrequently calcareous infiltration

FIG. 251.—HEART, ELASTIC MYOCARDITIS.

A. Endocardium greatly thickened and rich in elastica. *B*. Artery with enormous increase in elastica and proliferation in intima. Other vessels show similar changes. *C*. Vessel practically occluded by a thrombus.

is present, and the muscle-fibers usually show some granular change, and occasionally pigmentation. Interference with function is always probable; it may be slight, but in most instances dilatation comes on rapidly and gradual failure of the heart takes place.

Local or **circumscribed elastic myocarditis** does not differ conspicuously from the fibroid form; the distribution is essentially the same in both. The affected tissue is softer, lighter in color, and usually more vascular than in the purely fibroid type. When approaching the pericardium or endocardium, especially the latter, and when involving the columnæ carneæ, or papillary muscles, a bright, grayish, shiny appearance, resembling mother-of-pearl, is produced. Histologically the most striking feature is the enormous increase in the elastica. This substance

can be seen as rather coarse wavy fibrils, the direction of which corresponds to the course originally taken by the muscle-fibers.

Diffuse elastic myocarditis, in the milder cases, gives rise to no gross alteration. The muscle may be normal in color and elasticity; usually when pinched there is more resistance than in health. In some cases a slight grayish opacity is present beneath the endocardium, but often this is not marked; histologically the distribution of the hyperplastic elastica is more likely to be nodular and perivascular than the fibrous tissue of the dystrophic type. The origin of the newly formed elastic tissue is usually obscure; in some of the perivascular lesions it may be possible that it arises from the elastica of the blood-vessels. The relatively broad bands,

FIG. 252.—HEART, ELASTIC MYOCARDITIS.

Transverse section of a muscle column at the point where it joins the ventricular myocardium. *A*. What appears to be the remains of a central vessel. Around this are arranged the concentric laminæ of swollen and at points fragmented elastica. The fine granules between the strands are transverse sections of elastica disposed longitudinally. *B*, *B*. Thickened endocardium. At this point the section shows the elastica to be cut, for the most part, transversely. *C*. *C*. Points of hemorrhage immediately beneath the endocardium. The lower part of the field is occupied by altered myocardium. Many of the muscle-fibers are granular. some appear vacuolated, and the interstitial fibrous tissue is increased.

that can sometimes be seen immediately beneath the endocardium, could not result from proliferation of the elastica of the normal vessels, and, as Letulle suggests, must have arisen from the elastic skeleton of the myocardium. It is reasonable to assume that in elastic myocarditis the propulsive action of the heart is less disturbed than in the fibroid myosclerosis. The clinical histories of some of the patients support this suggestion. Occasionally both fibroid and elastic myocarditis are concurrent.

Aneurysm of the heart results from any of the preceding conditions which, at any one point, lessens the resistance of the cardiac wall. Bulging occurs, the wall of the aneurysm being either a saccular mass without constriction or a seperate cavity communicating with the ventricle by a definite opening. A specimen in the writer's laboratory possesses a sac as large as an egg, its wall being made up of the endocardium, a layer of fibrous tissue, and the pericardium; the cavity of the aneurysm communicates with the ventricle by a small opening near the apex about one centimeter in diameter. In over sixty per cent. of the reported cases the aneurysm is in the left ventricular wall, usually near the apex. Rarely, the aneurysmal dilatation begins in the septum. When the aneurysm is composed of a dilated pouch communicating with the ventricular cavity through a small opening, thrombi are not infrequently present. As a result of roughening in the wall of the aneurysm a thrombus may form, even when there is no evident opportunity afforded for stagnation of the blood. Sometimes the aneurysmal wall is intensely calcific. The author has observed a case in which the whole of the aneurysm was attached to the parietal pericardium, suggesting the possibility of pericardial adhesions dragging the fibroid wall outward, and in that way favoring the local dilatation, the cause of which must be principally the intraventricular pressure. Rupture occurs in many cases, and death almost instantaneously follows.

Diseases of the blood-vessels supplying the heart do not commonly differ from similar alterations observed in the arteries elsewhere. Although the coronary arteries are not without anastomoses, one with another, facilities for abundant collateral circulation are wanting and consequently obstructive or occlusive lesions are fraught with myocardial disaster, a fact previously discussed under chronic myocarditis.

Atheroma of the coronary arteries, *obliterative arteritis*, and fatty degeneration of the intima and media occur under the same conditions and from the same causes as observed elsewhere. Atheroma and obliterative change are frequently associated with syphilis, and may constitute a part of the fibroid change occurring in the organ in this disease. Atheroma as well as obliterative arteritis may lessen the carrying capacity of the vessel, lower the nutrition of the cardiac muscle in the area beyond, and favor the occurrence of fibroid change. Huchard analyzed 145 cases of *angina pectoris* in which the postmortem showed that in 128 of the cases the coronary artery was diseased.

Fortunately, the coronary arteries are rarely the sites of *thrombosis* and *embolism*. Atheroma and obliterative change favor the occurrence of thrombosis. Embolism is less frequent. With the occlusion of a branch of the artery, the nutrition of the area beyond is suspended, and later that portion of the myocardium involved undergoes necrosis terminating in rapid softening, the resulting condition constituting a form of what the older writers called **myomalacia cordis.** With the presence of infected emboli in the blood, and possibly as a result of mural implantation of bacteria circulating in the coronary vessels, metastatic abscesses are engendered in the myocardium. (See Embolism, p. 278; also Acute Suppurative Myocarditis, p. 495.)

Aneurysm of the coronary artery is rare. It may result from atheroma or degenerative changes in the arterial wall, and is said to occur as a result of inflammation or degeneration involving the adjacent

muscle. According to Griffith,[1] there are twenty-four cases of coronary aneurysm on record; in seven of the reported instances more than one aneurysm was present; in one case there were twelve. Death from rupture and consequent hemorrhage occurred in about half the cases.

Syphilis[2] of the myocardium may attack the blood-vessels, interstitial tissue, or muscle. The vascular lesion may be a gummatous arteritis or the ordinary type of arteriosclerosis. The changes in the vessels by altering the blood-supply may produce a secondary fibroid myocarditis. The last lesion sometimes occurs independently of marked coronary disease and may be diffuse or distributed in small nodes (miliary gummata) throughout the organ. A diffuse syphilitic degenerative change of the muscle-fibers of the heart has been described. A most striking manifestation of syphilis is the **cardiac gumma.** The older of these are gray, yellowish-gray, or hyaline, contain areas of necrosis which are sometimes caseous, and may attain a diameter of 3 cm. to 4 cm. The lesion is usually situated in the left ventricular wall, sometimes along the septum and rarely on the right side. Usually cardiac gumma is solitary. Amyloid infiltration and hyaline degeneration of the vessels and muscle-fibers may accompany syphilis. In hereditary syphilis diffuse fibroid induration is sometimes present and gummata have been described. Mraček and also Hektoen have reported instances of multiple foci of interstitial myocarditis due to hereditary syphilis.

Tuberculosis[3] of the heart may involve any part of the organ. Ferrand and Rathery, Oettinger and Braillon, and others have recorded instances of tuberculous endocarditis; Tessier was able to collect forty-seven cases in which endocardial lesions accompanied tuberculosis. Anders reported the seventy-second case of tuberculosis of the myocardium. It is doubtful if the heart is ever primarily affected, the involvement usually being secondary to pulmonary, peribronchial, or mediastinal tuberculosis. Anatomically the lesion may be of the miliary type, which necessarily represents a hematogenous infection. Many years ago Weigert expressed the belief that the heart was frequently involved in miliary tuberculosis. Tuberculous pericarditis, especially the caseous form, may infiltrate the myocardium. (See Fig. 241, p. 478.) The most frequent manifestation of cardiac tuberculosis is the large solitary caseous or calcareocaseous mass which may attain a diameter of 4 cm. to 5 cm. Any part of the heart may be affected, but in nearly half of the cases the lesion is in the left ventricle. The caseous mass is usually situated externally; the cardiac wall may be penetrated, and the cheesy material discharged into the blood-stream, giving rise to miliary tuberculosis. A diffuse fibroid myocarditis is sometimes seen

[1] "Brit. Med. Jour.," Feb. 2, 1901.

[2] Weber, "Med. Record," Aug. 29, 1903, p. 321. Adler, "Med. Record," Feb 20, 1904, p. 281. Cecikas, "Rev. de méd.," Dec., 1904. Stockmann, "Ueber Gummiknoten in herzfleische bei Erwachsenen," Bergmann, Wiesbaden, 1904. Romanov, "Roussk. Vratch," Nov. 6, 1904.

[3] Moser, "Med. and Surg. Reports of the Boston City Hospital," eleventh series, 1900. Crawford, "Edinburgh Med. Jour.," Sept., 1901. Heineman, "Lancet," Dec. 28, 1901. Anders, "Jour. Amer. Med. Assoc.," Nov. 1, 1902, p. 1081. Sotti, "Arch. per le Sc. med.," 1904, vol. xxviii. Raviart and Caudron, "Echo Méd. du Nord," Nov. 6, 1904. Silbergleit, "Virchow's Arch.," Feb. 1, 1905, Bd. 179, p. 283. Schwarz, "Centralbl. f. allg. Path. u. path. Anat.," April 15, 1905. Ferrand and Rathery, "La Méd. Mod.," Feb. 18, 1903. Oettinger and Braillon, "Soc. Med. des Hôp. de Paris," July 15, 1904.

in tuberculosis and has been attributed to the poison of the tubercle bacillus. Sotti has reported two cases of hemorrhagic tuberculous myocarditis; the lesion may be focal or disseminated throughout the organ.

Actinomycosis[1] **of the heart** is rare, is usually due to extension from a primary lesion in contiguous tissues, and may be attended by numerous fistulæ opening externally.

Tumors[2] **of the heart** are of infrequent occurrence. About forty instances of primary cardiac neoplasm have been reported. Of the 150 collected by Cornil, in 1902, secondary growths were ten times as frequent as the primary. **Sarcoma** is the most common of the primary neoplasms, although **rhabdomyoma, myxoma, fibroma,** and **chondroma** have been observed. Secondary tumors of the organ may result from extension from some contiguous viscus or mediastinal tissues. Most instances of secondary tumors of the heart due to extension have been from primary cancers of the esophagus. By the blood-stream, the cardiac tumor may be due to implantation among the muscle columns, or invasion by the coronary vessels. Propagated neoplastic thrombi may reach the heart by the larger veins. Statistics show that the tumor most likely to give rise to metastasis in the heart is sarcoma of bone. Most of the pedunculated tumors of the heart attached to the septum and projecting into the left ventricle are more or less perfectly organized cardiac thrombi.

Hydatid cysts[3] **of the heart** are rare; they may involve the myocardium or be embolic. In the cases recorded by Altmann and by Quill death resulted from embolic cysts blocking the pulmonary artery.

Rupture[4] **of the heart** may be traumatic or pathologic; I think we may exclude the so-called idiopathic, on the ground that the normal heart does not rupture. Ruptures resulting from blows on the chest, crushes, and falls are more frequent on the right side, and in the auricles, owing to the fact that the walls of these cavities are thinner than the left ventricle, and also because the right ventricle is so situated that it receives the brunt of any external injury transmitted through the anterior chest wall. The pathologic ruptures are due to diseases of the myocardium and usually (seventy-five to eighty per cent. of the cases) involve the left ventricle. Three-fourths of the pathologic ruptures are due to some form of fatty disease of the heart. Infarction, aneurysm, abscess of the myocardium, cysts, and tumors account for the remaining cases. The rupture may be *single* or *multiple*, *complete* or *partial*. As many as six or seven distinct ruptures may be present. With a rupture extending through the wall or from the pericardium nearly to the endocardium, or in the reverse direction, there may be purely intramural tears in the muscle, as shown by hemorrhages into the myocardium at the point of

[1] Schrotter, XX German Cong. Intern. Med. Wiesbaden, April, 1902.

[2] Geibel, "Centralbl. f. allg. Path. u. path. Anat.," 1899, x, 848. Curtis, "L'Echo Méd. du Nord," July 10, 1904. Sainmont, Thèse de Paris, 1903. Cagnetto, "Arch. per le Sc. Med.," 1904.

[3] Altmann, "Intercolonial Jour. of Australasia," Dec. 20, 1902. Davies, "Hydatid Disease," 1894. Masovic, "Wien. med. Woch.," 1904, No. 9. Quill, "Jour. of Royal Army Med. Corps," April, 1904.

[4] Ercklentz, "Zeit. f. klin. Med. Berlin," xliv, Nos. 5 and 6. Grout, "Amer. Med.," April 12, 1902. Revenstorf, "Mittheil. a. d. Grenzgeb. d. Med. u. Chir.," Bd. xi, H. 4, p. 603. Hamilton, "Phila. Med. Jour.," Jan. 24, 1903. Foott and Hall, "Lancet." Jan. 16 1904, p. 152. Winkler, "La Presse Méd.," Feb. 22, 1905, p. 117.

rupture. Ruptures are not inevitably fatal; and even when multiple, death may be delayed for days or weeks. A rupture of sufficient size, to permitt rapid evacuation of the ventricle, leads to sudden death. In the smaller ruptures, that leak but little, recovery is possible. The great obstacle to recovery from rupture of the heart is the fact that the conditions upon which the lesion usually depends lessen the reparative power of the organ.

Wounds[1] **of,** and **foreign bodies**[2] **in, the myocardium** are tolerated by the organ about as well as similar lesions are borne by other structures. Peck has been able to collate 160 cases of cardiac wound operated upon, with recovery in 36.3 per cent. The dangers are shock, hemorrhage and infection, and, if these can be avoided, cicatrization is accomplished with little difficulty. Regeneration of the myocardium can not be expected. Foreign bodies are occasionally present in the heart without giving rise to any symptoms. Bullets healed in the heart wall have been reported by Riethus, Brown, and others. Brown's patient carried an old-time musket ball in the myocardium of the left ventricle for thirty-six years. The bullet may be free in the ventricular cavity; but usually, when so situated, it becomes entangled in spaces between muscle columns and is attached by a thrombus which finally organizes.

ENDOCARDIUM.

The surface of the *normal endocardium* is composed of a flattened layer of endothelial cells—histologically, a serous membrane. The continuous flow of blood over its surface, and the difference in function from other serous membranes, render a separate description of its diseases necessary. The membrane is nonvascular even in its reflected layers, which, reinforced by fibrous and elastic tissues, form the valves. The latter structures are rich in lymphatics, through which the nourishment of the supporting framework is maintained. Recent investigations seem to show that the bases of the mitral and tricuspid leaflets contain some capillary ramifications; the blood-vessels do not, however, approach the free edges of the valves. Immediately beneath the endocardium ramifies the plexus of nerves described by Krause.

INFLAMMATION OF THE ENDOCARDIUM—ENDOCARDITIS.[3]

General Considerations; Classification.—That part of the endocardium sustaining the most stress, other things being equal, will first suffer and suffer most. Recognition of this fact explains the infrequency of the process on the right side in adult life, and the rarity of intrauterine disease of the left side; it elucidates those cases of secondary endocardial inflammation of the right side, in adult life, when extensive obstructive or regurgitant lesion of the left side raises the tension and increases the work of the right heart. When inflammation involves the

[1] Peck, "Annals of Surgery," July, 1909.

[2] Editorial, "Phila. Med. Jour.," April 27, 1901. Brown, "Trans. West Virginia Med. Assoc.," 1902, p. 720. Riethus, "Deut. Zeit. f. Chir.," vol. lxvii. Fischer, "Deut. med. Woch.," Aug. 28, 1902. Koch, "Berl. klin. Woch.," 1904 July 11, No. 28.

[3] Thorel, "Lubarsch and Ostertag's Ergebnisse d. allgem. Path. u. path. Anat.," 1903, Neunter Jahr. I. Abt., p. 683.

valvular endocardium, the condition is known as **valvular endocarditis**, or **valvulitis**; when the auricular or ventricular wall is affected, it is called **mural endocarditis**; the latter is rare except in the malignant and atheromatous forms. In the adult about one-half of the cases of endocarditis attack the mitral leaflets; of the remaining fifty per cent., about ninety-four per cent. involve the aortic cusps; the remaining cases are divided between the valves of the right side, the tricuspid being the more commonly affected.

Inflammation of the endocardium may be *acute* or *chronic*. It has been customary for pathologists and clinicians to divide the acute inflammations of the endocardium into *simple* and *malignant*. It was believed that the acute simple endocarditis was noninfective in origin, and that it was not associated with the presence of bacteria. The tendency at present is to regard both forms as dependent upon infection, but in that type previously called simple endocarditis, the infection differs in degree, or possibly in character, from that seen in the ulcerative variety Both pathologically and clinically, cases are not infrequently seen in which the clinical history and morbid anatomy justify the term simple endocarditis. It is equally true that we occasionally find extensive lesions, affecting the valves and mural endocardium, associated with pyogenic infection, and also, although less commonly, with other mycoses, clinically and anatomically meriting the name ulcerative or malignant endocarditis. Between these extremes there is a middle ground, occupied by a not very small number of cases, in which it is quite impossible, either anatomically or clinically, to separate and group them with one or the other of the foregoing divisions. The possible identification of differences once believed to be clearly recognizable is further complicated by the more recent introduction of the term acute malignant rheumatic endocarditis,[1] and applying it to a form of endocardial inflammation of rheumatic origin, usually terminating fatally, without the tendency to suppurative lesions in other viscera, and unassociated with the rather characteristic temperature-curve of that form of endocardial inflammation that we have been in the habit of calling malignant endocarditis. It is to be presumed that the easily recognized differences between the typical, clearly defined, acute, simple endocarditis and the admittedly malignant endocarditis must depend upon the character of the infection and upon the resistance of the tissues to the infective agent. Thus, infection manifested by the presence of staphylococci will usually be ulcerative in type, while the endocardial inflammations accompanying rheumatism rarely assume the general characters of the ulcerative form of endocarditis. Bearing the foregoing facts in mind, and remembering that the so-called acute simple endocarditis may or may not terminate in the malignant, I shall adhere to the customary division, based upon the belief that it is possible to recognize an *acute simple endocarditis* and an *acute malignant endocarditis*.

The *chronic*, *indurative*, *sclerotic*, or *interstitial endocarditis* is still to be regarded as an entity, although it often is nothing more than a terminal stage of an acute process.

[1] Litten, "Berl. klin. Woch.," 1899. The same observer, more recently ("Deut. med. Woch.," May 22 and 29, 1902), has proposed to divide acute endocarditis into (1) benign, (2) septic ulcerative, (3) nonseptic ulcerative. In the latter form evidence of ulceration is present, but patients do not manifest the usual phenomena of sepsis.

Acute Simple Endocarditis.—*Causes.*—The most frequent cause of this form of endocarditis is acute articular rheumatism.[1] Litten's statistics show that in 30,000 patients there were 400 cases of endocarditis, thirty-five per cent. of which were due to rheumatism. Although there may be some doubt as to the specificity of the organism found in rheumatism, the infectious nature of the disease is generally accepted. Frequently endocarditis is preceded by tonsillitis, and, as this may be rheumatic, such cases belong with those due to the first-mentioned group of causes. The fact that in some cases of endocarditis following tonsillitis other bacteria have been observed indicates that the tonsil[2] may be the portal through which infection occurs in types of the affection other than pure rheumatic endocarditis. The endocarditis accompanying or following pneumonia[3] and due to the pneumococcus is sometimes of the form at present under consideration; often, however, it resembles the ulcerative or malignant type. Kerchensteiner believes that pneumococcus endocarditis is, anatomically, midway between the verrucose and ulcerative forms. Endocarditis of this type may follow other acute infectious diseases,[4] among which should be mentioned diphtheria,[5] scarlet fever,[6] mumps,[7] influenza,[8] and erysipelas. The association of endocarditis and chorea[9] is probably due to the fact that in certain instances both are infectious diseases; streptococci have been isolated from the blood in a number of these cases. Debilitating diseases that depress the antimicrobic functions are frequently accompanied by endocarditis; among such affections should be mentioned gout, diabetes, and renal disease and degeneration, especially chronic interstitial nephritis. The relation of trauma[10] to acute and chronic lesions of the endocardium has been variously estimated; there are, however, undoubted instances in which valve rupture and subsequent inflammation have followed violent exertion and chest injuries. Pleasants has been able to collect fourteen cases of endocarditis believed to have been of traumatic origin; to these the three reported by Sinnhuber should be added. In a few cases endocarditis had resulted from transplacental infection.[11] Previous attacks increase susceptibility to the disease. Robinson[12] has been able to collect seventeen cases of acute endocarditis associated with congenital malformation of the heart.

[1] For references see second foot-note, p. 112; also consult Lewis and Longcope, "Amer. Jour. of Med. Sci.," Oct., 1904, p. 601. Harrass, "Münch. med. Woch.," Aug. 30, 1904. Cole, "Jour. of Infect. Disease," Nov. 5, 1904, p. 714.

[2] Gurich, "Münch. med. Woch.," Nov. 22, 1904.

[3] Preble, "Amer. Jour. of Med. Sci.," Nov., 1904, p. 783; full bibliography.

[4] Weaver, "Ft. Wayne Med. Magazine," Nov., 1904.

[5] Jump, "Pediatrics," Aug., 1903.

[6] Spencer, "Lancet," Feb. 19, 1905, p. 420.

[7] Tatschner, "Wien. med. Woch.," July 30, 1904.

[8] Flexner, "Univ. of Penna. Med. Bull.," Jan., 1903, p. 551; also Escudero, "Argentina Med.," Nov. 19, 1904.

[9] Hirshberg, "Jour. of the Alumni Assoc. of the College of Physicians and Surgeons, Baltimore," April, 1903.

[10] Pleasants, "Bull. of Johns Hopkins Hosp.," 1903, vol. xiv, p. 124. Libman, "N. Y. Path. Soc.," Oct. 8. 1902. Strumpler, "Münch. med. Woch.," July 14, 1903. Sinnhuber, "Deut. med. Woch.," 1904, xxx, No. 32, p. 1161.

[11] Ballantyne, "Manual of Antenatal Pathology and Hygiene." Fisher, "Reports of the Society for the Study of Diseases in Children," 1902, vol. ii.

[12] "Bull. of the Ayer Clinical Laboratory of the Pennsylvania Hospital," Jan., 1905, No. 2, p. 45.

At the present time few doubt the infectious nature of acute endocarditis. A number of bacteria, mostly micrococci, have been found in the valves and superimposed vegetation. Apparently the same organisms occur in the so-called acute simple endocarditis and the malignant forms of the affection. The clinical and anatomic differences between the two classes probably depend upon the pathogenic capacity of the organism or the varying susceptibility of the infected patients. All forms of acute endocarditis are constantly associated with morbid processes admittedly of microorganismal origin, and an extended study of the affection, by recent methods, has led to the frequent isolation of bacteria from the blood during life and from the cardiac lesions post-

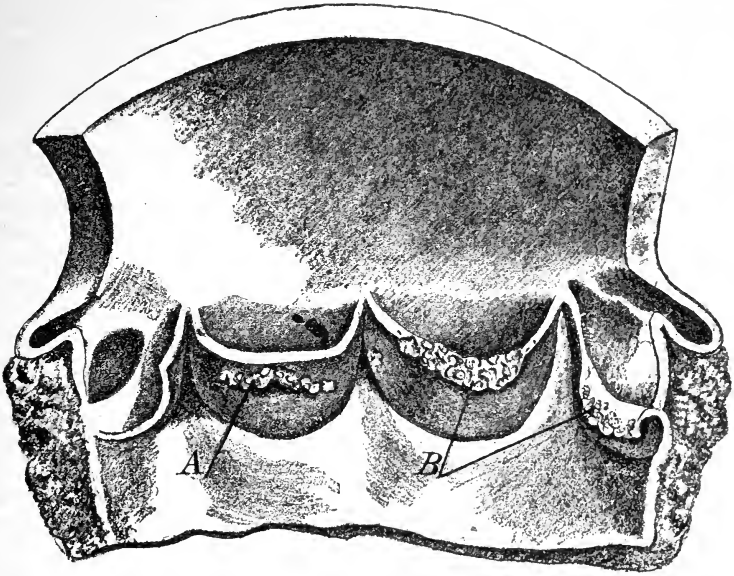


FIG. 253.—AORTIC ORIFICE LAID OPEN, SHOWING THE VALVE LEAFLETS, ACUTE ENDOCARDITIS.—(*Redrawn from Schmaus.*)

A. Line of contact with beginning formation of vegetations. *B*. More advanced and larger vegetations closely simulating in appearance an ulcerative lesion. Between the leaflet *A* and the leaflet immediately above the letter *B* is seen a single vegetation on the leaflet *B;* should a similar lesion occur at the corresponding point on the leaflet *A*, the two, coming together, could coalesce, or the continued deposit of fibrin might fuse the adjacent masses, and, by organization, would produce an adhesion between the two leaflets, thereby narrowing the orifice.

mortem. The attempts to establish a specific organism for endocarditis have been unsuccessful.

Heiberg and Winge in 1869 demonstrated bacteria in the lesions of endocarditis. Harblitz[1] analyzed the records upon the subject, and believed that it might be possible to differentiate some of the infections by the character of the lesion; streptococcus infections produce large vegetations that progress slowly and are accompanied by nephritis. In the pyemic endocardial lesions containing the ordinary staphylococci the course of the disease is usually more rapid, the valve destruction

[1] Harblitz, "Om Endokardit, dens Pathologiske Anatomi, og Aetiologi," 1897. Harblitz, "Deutsch. med. Woch.," Feb. 23, 1899.

greater and associated with more wide-spread infection. Extended observations have shown that the morbid anatomy is insufficient to differentiate the lesions produced by one germ from those due to other bacteria, and that the same microbe may be found in both ulcerative and verrucose types of the affection.

In addition to the Diplococcus rheumaticus,[1] the organisms usually found in endocarditis belong to the pyococcic group, and include the staphylococci, streptococci, pneumococcus, and gonococcus.[2] According to Preble, there are one hundred and thirty-two reported cases of pneumococcus endocarditis. Many accurately observed instances of gonococcal endocarditis[3] are on record. Among the organisms less frequently found are the colon bacillus, bacillus of Friedländer, Bacillus typhosus, Bacillus diphtheriæ, Micrococcus endocarditidis rugatus (Weichselbaum), Micrococcus endocarditidis capsulatus (Weichselbaum), Micrococcus zymogenes, Bacillus endocarditidis griseus (Weichselbaum), Bacillus endocarditidis capsulatus, and the tubercle bacillus. Warfield and Walker[4] report a case of acute ulcerative endocarditis due to the meningococcus.

FIG. 254.—ACUTE ENDOCARDITIS OF THE MITRAL VALVE, SECTION AT LINE CONTACT. (Partly diagrammatic.)—(*Rindfleisch.*) × 10 diameters.

a a'. Endocardium, which at *c* has become swollen and abraded and covered by the cap of fibrin, *d*. *b*. Interstitial tissue of the valve with newly formed blood-vessels. *e*. Free margin of valve leaflet.

Morbid Anatomy.[5]—The alterations observed in this condition may be more or less arbitrarily divided into two stages, the first of which terminates with the formation of vegetations. Redness and injection are not present, as the tissue is nonvascular. (*a*) The milky opacity of the membrane is due to serum and leukocytes infiltrating the lymph-spaces of the affected leaflet, and to slight roughening of the endothelial surface; the latter change produces an effect similar to that which results from grinding the surface of glass. (*b*) Bogginess or edema of the valve is discernible at this time, and is due to the infiltration of the valve tissue by serum and leukocytes. In this softened and boggy condition, the valves pounding against one another at the rate of from 120 to 150 times a minute, (*c*) abrasion or even laceration may occur. The line of friction is the line of contact, and along this line the roughened points develop. A microscopic examination of the valve in this stage shows more or less necrosis of the endothelium, associated with desquamation, and in some cases hyaline degeneration or distinct coagulation necrosis. The subendocardial connective-tissue cells and fibrils are not infrequently swollen, and the lymph-spaces of the valve may contain fibrin. The elastica of the affected leaflet is swollen and may be fragmented.

The Production of Vegetations.—The blood passing over the roughened line of abrasion deposits a cap of fibrin upon the rough points; to this are added cells produced by proliferation of the connective-tissue

[1] See p. 112.
[2] See p. 107.
[3] Harris and Johnston, "Bull. of Johns Hopkins Hospital," 1902, vol. xiii, p. 236. Thayer, "Amer. Jrnl. of the Med. Sci.," Nov., 1905.
[4] "Bull. of the Ayer Clinical Laboratory of the Pennsylvania Hospital," Oct., 1903, No. 1, p. 81.
[5] For the histology of endocarditis see Koniger, Arbeit. a. d. Path. Inst. Leipsic, 1903.

elements and a further infiltration of the affected valve by leukocytes. These changes are most marked beneath the area of roughening, and increase the size of the so-called vegetation or cap of fibrin. The deposited fibrin may be granular, fibrillar, or, less frequently, hyaline. The distinctly hyaline form of fibrin is rarely present; when found, it occurs as small irregular collections in the forming vegetation. It should be observed that structurally and genetically the developed vegetation is essentially a thrombus. It may contain all the bodies commonly found in thrombi,—fibrin, leukocytes, erythrocytes, and platelets,—and is subject to secondary changes identical with those occurring in thrombi. (See Thrombosis, p. 270.)

With firm vegetations of moderate size the lesion is called **endocarditis verrucosa**; when the collection of fibrin is large and flabby, the term **polypous** or **villous endocarditis** is at times applied.

Changes in the Fibrin Cap or Vegetation.—The vegetation sometimes increases by layers and may, in this way, become distinctly stratified; it may be redissolved. As a result of its large size vascularization, and consequent organization, are often impossible; the bacteria present, or their toxins, may cause softening (further necrosis) which terminates in fragmentation, the resulting particles constituting emboli. If near a corresponding mass, on an apposed leaflet, especially at the valvular attachment, cohesion of two vegetations may constitute the preliminary step in the formation of an adhesion (see Fig. 256). Organization of the mass is the last process, and by some is considered as a third stage. Unless the inflammation be fulminatingly rapid, organization has begun, at the point of attachment to the valve, by the time the vegetation is visible to the unaided eye; as organization progresses, new blood-vessels develop from the base of the valve, are projected into the leaflet, and finally enter the vegetation at its point of origin. The presence of

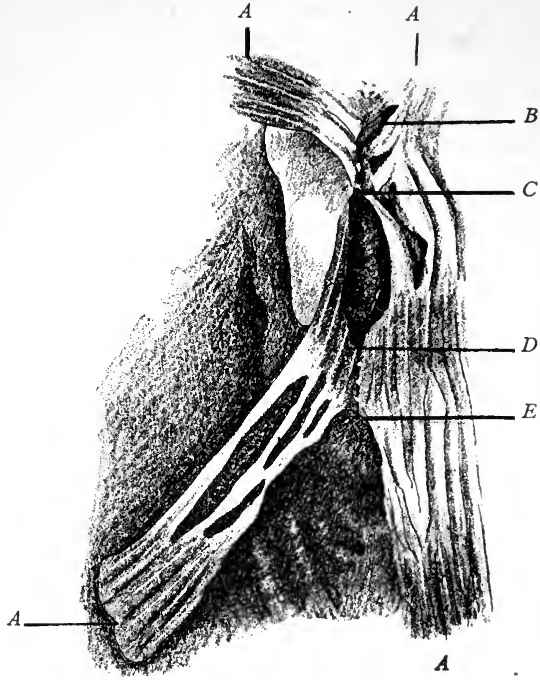


FIG. 255.—NARROWED MITRAL ORIFICE, SHOWING RESULTS OF ADHESIONS WITH CONSIDERABLE FIBROID THICKENING (BUTTON-HOLE MITRAL).

A, A, A, A. Papillary muscles and tendons. *B* to *C*. Area of adhesion and fibroid thickening. *D* to *E*. Second area of adhesion and fibroid thickening. The whole free margin of the valve is intensely indurated, rendering the leaflet too stiff to close readily and, as a result of the adhesions, unable to open its normal lumen, giving rise to both stenosis and regurgitation.—(*From specimen in author's collection.*)

sufficiently active pyogenic and some other bacteria may limit or prevent organization and give rise to disintegration and softening.

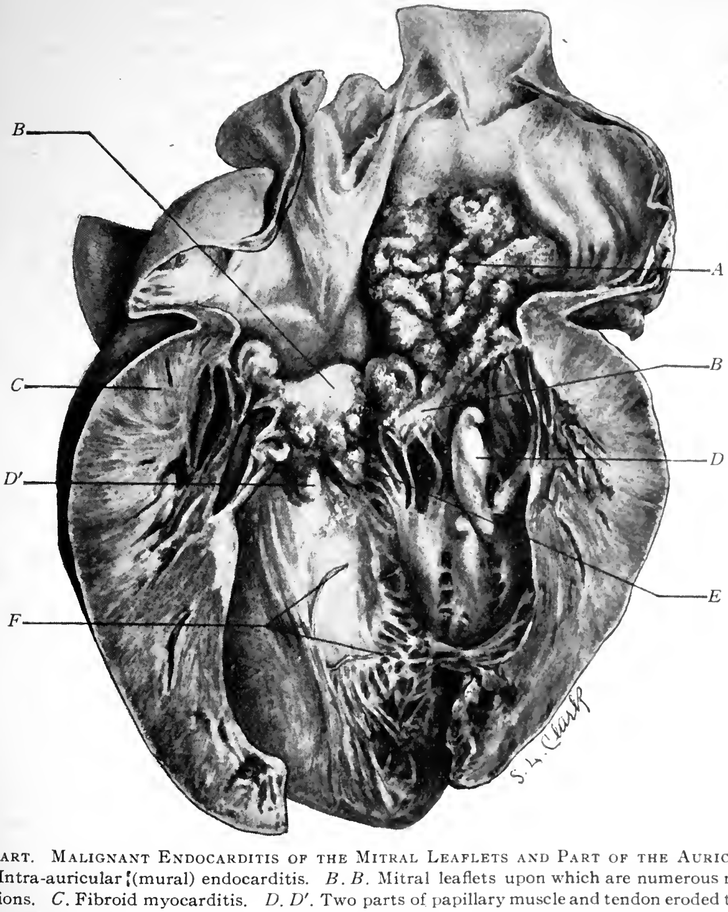
The influence of these changes upon the structure and functions of the affected valve may be epitomized as follows: (1) At an early stage the thickening or swelling muffles the valves and alters the sounds produced by their closure; (2) if not prevented by the cap of fibrin a hole may be torn in the valve (fenestration), or traction by the flowing blood on a large or loosely attached vegetation may pull it away, giving rise to a fenestrum at the point from which the fibrin mass was detached; (3) laceration of the valve leaflet, a further process than fenestration; (4) adhesions of valve leaflets (see Fig. 256); (5) induration, as organization occurs; (6) contraction of the valve (see Fig. 255); (7) calcareous or atheromatous changes (see Fig. 256); (8) dilatation of the valve or orifice may occur early, from the softening and edema of the initial stage, or it may follow the atheroma; (9) a single valve leaflet may relax, producing what is sometimes termed an *aneurysm of the valve.*

Acute Malignant Endocarditis.[1]—(Synonyms, *Ulcerative*, *Mycotic*, *Bacterial*, or *Pustular Endocarditis; Arterial Pyemia; L'Endocardite Vegetante Ulcereuse; Endocarditis Pyœmica; Diphtheric Endocarditis*, etc.)

Causes.—As intimated when discussing the classification of endocarditis, the ulcerative variety possesses no causative factors that distinguish it from the milder form just described. The bacteriology of the two conditions is essentially similar, although in cases assuming the virulent type pneumococcic, streptococcic, and other pyococcic infections are the commonest. The disease is frequently associated with pyemia, septicemia, croupous pneumonia, puerperal and wound infections, abscesses, osteomyelitis, and other processes in which the pyogenic bacteria are usually found. The simple form of endocarditis may gradually develop into the malignant type. Malignant endocarditis is particularly prone to involve the sclerotic valves; Orth holds that it never affects previously sound tissue, and the number of cases examined postmortem in which the acute lesion was engrafted on sclerotic leaflets differs in the collected series of cases, but is always high, ranging from sixty to eighty-eight per cent. Occasionally it is secondary to myocardial infection, particularly when the latter results from infective embolism of the coronary artery.

Ulcerative endocarditis may affect (1) the contact line of the valves, (2) base of a leaflet, or (3) it may be mural. As to orifice, Osler, Sansom, and Hamilton accept the following order: (1) Mitral; (2) aortic; (3) aortic and mitral; (4) heart-wall; (5) tricuspid; (6) pulmonary. The valves of the right side of the heart are more frequently affected in this form of endocardial inflammation than in the acute simple endocarditis. This is to be explained by the fact that in such infectious diseases as suppuration, erysipelas, osteomyelitis, puerperal fever, and other infections involving the genito-urinary organs, ulcerations of the intestine, suppurative processes in the liver, and otitis media, the venous blood returns to the heart charged with the bacteria, and hence the valves

[1] Herrick, "Northwestern Lancet," March 15, 1902. Lenhartz, "Münch. med. Woch.," July 9, 1901. Robinson, "Amer. Jour. of Med. Sci.," April, 1904, p. 623. French, "The Practitioner," Dec., 1904, p. 753. Coleman, "Amer. Jour. of Med. Sci.," March, 1905. Thorel, "Lubarsch and Ostertag's Ergebnisse d. allgem. Path. u. path. Anat.," 1903, Neunter Jahr. I. Abt., p. 718.



HEART. MALIGNANT ENDOCARDITIS OF THE MITRAL LEAFLETS AND PART OF THE AURICLE.

A. Intra-auricular (mural) endocarditis. *B. B*. Mitral leaflets upon which are numerous necrotic vegetations. *C*. Fibroid myocarditis. *D. D'*. Two parts of papillary muscle and tendon eroded through and separated by the progressing necrosis. *D*. Partly necrotic papillary muscle separated from the tendon. *D'*. Tendon attached to valve. *E*. Large mass of vegetation which had retroverted into auricle and, by friction against wall, inoculated the surface. *F*. Attenuated muscular column that has eroded through.

first subjected to the danger of infection are those of the right side. Following Virchow, most observers believe that the infection is the result of direct implantation of bacteria upon the valve segments, although Köster has strongly urged the possibility of infection through the blood-vessels of the leaflet. The almost complete absence of blood-vessels in the normal leaflet, and the fact that bacteria are most abundant in the periphery of the lesion, would favor the view first given; Köster's contention is supported by the frequency with which the disease affects valves vascularized as the result of antecedent inflammation.

Morbid Anatomy (Plate XII).—Whether preceded by simple inflammation or not, necrosis, ulceration, and loss of tissue are almost constantly present. Ulceration in the sense that a distinct recognizable or anatomically perfect ulcer must be developed is not at all necessary. Bacteria are invariably present during the active stage of the process, and are usually most abundant in the superficial layers of the vegetation, although they are not infrequently found at the bases and in the interstices of the valves. Vegetations are usually large, although well-marked cases have been reported in which they were small. They usually manifest evidences of necrosis, softening, and fragmentation. As a result of these changes, embolism, with the development of suppurative processes in other viscera, usually accompanies this form of endocarditis. The necrotic processes are not restricted to the vegetation alone, but may involve the affected leaflet, which is sometimes totally destroyed. Mural lesions are not infrequent; they sometimes depend upon direct inoculation from bacteria in the blood; in other cases their location would indicate that the vegetation had, by contact, inoculated the ventricular, auricular, or aortic wall. Cases occur in which it is possible to believe that the infection involved the heart muscle as a result of dissemination through the blood by way of the coronary artery.

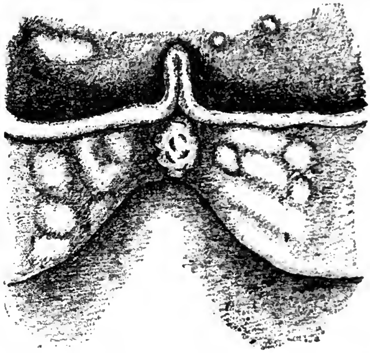


Fig. 256.—Adjacent Aortic Cusps, Showing a Small Vegetation Developing Just Below the Point of an Old Adhesion.

Calcareous areas are indicated by the white areas on the valve leaflet. A case of acute endocardial inflammation ingrafted on chronic lesion.

Microscopic abscesses are sometimes to be recognized in the valve tissue, and similar areas of a larger size are occasionally observed in the myocardium. The extension of the infection to the myocardium may lead to penetration or perforation of the ventricular septum, aneurysm, or rupture of the heart. The calcific deposits occasionally observed in this form of endocarditis may be due to the fact that the lesion is ingrafted upon an old endocardial change in which calcification was present. In other instances there is reason to believe that the infiltration is secondary to the acute process with which it is found.

The structural alterations produced by this form of endocarditis are often striking; entire leaflets may disappear and penetration of the cardiac septa may give rise to abnormal communication between the

cavities. The disease is often rapidly fatal, although Herrick's contention that many typical cases recover is now generally accepted. The rapid formation and prompt necrosis of vegetations induce a constant change in the morphology of the affected valves and fibrin masses, resulting in sudden alterations in the physical signs, usually absent in other types of endocarditis. In some cases the symptomatology is largely restricted to the heart manifestations; this form of the affection is called the *cardiac type*. In other instances the symptomatology is not unlike typhoid fever (*typhoid type*). In the *pyemic* or *septic type*, the phenomena are those of pyemia or septicemia; embolism and metastatic abscesses are not infrequent. In some cases definite febrile paroxysms, during which the temperature rises sometimes from 5° C. to 6° C., occur (*pseudomalarial type*). These phenomena are due to the influence of bacterial toxins, derived from the lesions in the heart, or resulting from the pullulation of bacteria in the blood-stream. Septic inflammations of the joints are not uncommon; endarterial infection which may terminate in aneurysm, and rupture of the affected vessel sometimes occurs; these and other indications of a widely distributed infection justify the name *arterial pyemia* given to the condition by the older writers. Some of the cases belonging to the cardiac type may drag along for weeks or even months (**chronic ulcerating endocarditis**); French refers to an instance in which the illness lasted 297 days. In the cases that recover there is usually marked valvular distortion, which may also involve the orifice, permanently crippling the heart.

Chronic Endocarditis.—(Synonyms, *Indurative*, *Fibrous*, *Sclerotic*, *Adhesive*, *Interstitial*, or *Permanent Endocarditis* and *Arteriosclerotic Valvulitis*.)

Chronic induration of the cardiac valves may result in a number of conditions; as already indicated, the acute forms of endocarditis may leave the valves irreparably damaged, the leaflets thickened, the margins irregular and indurated and sometimes adherent. It is not improbable that minor structural alterations in the leaflets may constitute a basis upon which a chronic sclerosing process is implanted. In many cases, however, this condition occurs without any antecedent endocarditis. It is particularly associated with affections in which persistent high tension occurs. Roy and Adami showed that if the aortic pressure be raised by constriction of the aorta, edematous blebs might develop in the aortic leaflets at points corresponding to the location of the most characteristic lesions of chronic fibroid valvulitis. It is probable that this, in a way, explains the influence of increased stress on the valve leaflets in man. The hypertension associated with arteriosclerosis and contracted kidney is a frequent cause. This form of valvular disease is often seen in syphilitics and in the gouty, and is common in alcoholics. Valvular sclerosis is rare, although not unknown, in youth, and occurs with increasing frequency in each decade after the fourth. It is so constantly associated with degenerative changes in the vessels that it has been called *arteriosclerotic valvulitis*.

Morbid Anatomy.—Chronic sclerotic changes occur in both mural and valvular endocardium; in the former the change is rarely intense. The valves and orifices commonly affected are those of the left side of the heart; sclerosis of the tricuspid and pulmonary leaflets is exceedingly rare. The first change observed is a grayish opacity, usually developing

along the line of contact and, on the aortic leaflets, often radiating from the corpora arantii. Sometimes the thickening forms distinct lines, parallel with the free edge, giving the surface of the valve a rippled appearance. Occasionally the valves remain pliable, constituting the soft variety of chronic valvulitis. Histologic examination of such structures shows that the new tissue is mostly elastica; this type is of infrequent occurrence and the lesion is rarely marked. The dense or hard form is more common. Histologic examination, in the earlier stages, discloses a marked connective-tissue hyperplasia, scantily supplied with fibroblasts. The interstitial fibroid change develops slowly, and gradually extends. It increases the thickness and lessens the pliability of the valve, sooner or later contracts, and undergoes calcareous change. (See Plate XI, Fig. 2.) The newly formed fibrous tissue frequently shows necrotic and degenerative processes, and, when fully developed, commonly contains areas of calcareous infiltration. Degenerative and necrotic changes in the overlying endothelium may expose the calcareous plaques; the presence of projecting spicules of calcific matter leads to a deposit of blood-platelets followed by fibrin, so that, even in this form of endocarditis, small fibrinous collections (vegetations) are occasionally seen. As contraction progresses, curling of the valve edges, insufficiency, and stenosis commonly develop. In figure 253 the valve leaflet on the extreme right is beginning to show slight eversion. The chordæ tendineæ thicken, agglutinate, or shorten, so that the muscle may appear to be inserted immediately into the valve cusp; narrowing, marginal thickening, and adhesion lead to such conditions as the button-hole mitral, funnel mitral, etc. As the sclerosis advances, the calcific changes become more marked, and eventually the valves and margins of the orifices are converted into hard, calcareous, fibroid structures, with scarcely a normal element remaining. The mural form of chronic endocarditis is secondary to atheroma or interstitial myocarditis, and is manifested by the presence of hard, fibroid, or calcareous areas on the cardiac wall.

FIG. 257.—ADHERENT AND THICKENED VALVE LEAFLETS.—(*Rindfleisch.*)
View obtained by looking downward upon the aortic valves from the aorta. Two leaflets are adherent, all are contracted, thickened, everted, and unable to open widely or close tightly.

Results of Endocarditis.—When the valve does not return to the normal, which in rare cases may occur, the changes already described lead inevitably to one of two conditions or to both.

1. *Narrowing, Obstruction, or Stenosis.*—This condition may be brought about in any of the following ways: (*a*) Vegetations projecting into the lumen when the valve is open; (*b*) stiffened valves that do not open; (*c*) contracted valves that can not open, but subtend the orifice like a cord; (*d*) adherent valves, the adhesions preventing opening; (*e*) eversion or inversion of a leaflet either as a part or as a whole; (*f*) a lacerated leaflet hanging in the current; (*g*) contraction of the orifice incident to a circumferential inflammation at the base of the valve, or in the mitral, the free margin; (*h*) loss of elasticity of the orifice, owing to fibrous or calcareous changes, or to both, without of necessity contracting, but being inelastic, is practically a stenosis; (*i*) combinations of these processes.

2. *Insufficiency or Incompetency of the Valves, Permitting Regurgitation.*—(*a*) Valves may be propped open by a vegetation; (*b*) valves may be too stiff to close; (*c*) contracted valves can not close, for the same reason that they can not open; (*d*) inverted, everted, or lacerated valves can not close the orifice; (*e*) fenestra below the line of contact permit regurgitation; (*f*) contraction of the orifice leading to wrinkling of the leaflets is by some supposed to be a cause; (*g*) relaxation, distention, or dilatation of the orifice beyond a size that the valve can close. This condition is called relative insufficiency and may be due to relaxation of the opening without any disease of the endocardium.

Influence of Stenosis and Insufficiency on Cardiac Work.—It matters not which of the above processes occurs, the inevitable consequence will be increased work for the heart, and this must lead to either hypertrophy or dilatation. It is not possible, in the space available, to consider the physics of the normal circulation, with which it is presumed that the student is familiar, nor can the disturbance brought about by stenosis and insufficiency be fully reviewed. It is, of course, evident that either of these conditions affecting the orifice through which the ventricle is normally emptied, more profoundly influences the function of that structure than when the process involves the orifice through which the cavity is filled. With the occurrence of aortic stenosis the work of the left ventricle must be increased, as it necessarily requires more force to deliver 100 gm. of blood through an orifice 50 mm. in circumference than through an orifice possessing a circumference of 70 mm. Were not so many factors to be taken into consideration, it would be possible theoretically to calculate the amount of increase in cardiac work that would result from a one-tenth reduction in the sectional area of the aortic orifice. The cardiac work is also increased by insufficiency or regurgitation, for if 100 gm. of blood has been delivered into the aorta during the previous systole, and if 25 gm. returns to the ventricle by reason of insufficiency in the aortic valves, the ventricle at the same time receiving its normal inflow from the auricle, it must be apparent that, in order to assure its progress, one-fourth of the blood is being pumped into the aorta twice. It of necessity follows that the heart is doing one-fourth of its work over, which, of course, implies an enormous increase in cardiac labor. The same hypotheses applied to the auricles would not yield the same conclusions; the auricular cavities communicate directly with their respective venous systems, so that the venous system of the side in question must always be considered practically as a part of the auricle. Nevertheless, it is evident that regurgitation through the mitral orifice must increase the work of the heart, as when the left ventricle contracts, a part of its force loses its effectiveness through the fact that the insufficient mitral permits a backward flow into the auricle. During the next diastole the ventricle should receive its normal quota of blood plus the blood that was regurgitated into the auricle through the insufficiently guarded mitral. This, of course, means increased work for the ventricle. Mitral stenosis acts differently,—at least, when marked,—as already referred to when considering local atrophy of the heart. (See p. 488.) In the presence of increased cardiac work brought about in ways that have just been mentioned, hypertrophy or dilatation must of necessity follow.

HYPERTROPHY AND DILATATION.

Hypertrophy—	*Dilatation*—
Simple.	[Simple.]
[Eccentric.]	With thickening.
[Concentric.]	With thinning.

Simple hypertrophy is increased weight with increased functional power, without evident alteration in the size of the cavity.

Eccentric hypertrophy is assumed to be increased weight, with increased (?) functional power and increased cavity; in other words, it is the same as *dilatation with thickening;* during life the symptoms, if any presented themselves, were those of dilatation rather than hypertrophy.

Concentric hypertrophy is assumed to be hypertrophy at the expense of the cavity: that is, increased weight, etc., with diminution in the size of the cavity. It is a postmortem change, or is dependent upon the conditions that determine death. Allbutt refers to it as a "mythical type" of hypertrophy. How easily one may be misled is illustrated by the following experiment:

Obtain three bullocks' hearts immediately on slaughtering. In one heart all the vessels should be ligated before the animal is bled or the vascular system opened; let the second heart remain empty. The third heart is to be distended by ligating the pulmonary veins, sectioning the aortic valves, and attaching the aorta to a hydrant. It is best that all the hearts possess about the same weight. In a few hours, when rigor mortis has ceased to act, the following will be found: The first heart is an example of hypertrophy with a normal cavity; the second, hypertrophy with diminished cavity; the third, hypertrophy with increased cavity. Death may arrest the heart in any degree of distention, or rigor mortis act to any extent, consequently any one of the foregoing conditions may be found in any hypertrophied heart examined postmortem. Simple hypertrophy therefore remains.

Dilatation with thickening is admitted, as is **dilatation with thinning;** but *simple dilatation* implies a larger cavity, with wall of normal thickness, and as such a heart must weigh more, it requiring more muscle to surround a large cavity with a wall of a given thickness than a smaller cavity, as the normal, the condition is one of dilatation with increased weight or thickening.

Causes of Hypertrophy and Dilatation.—Increased work with abundant nutrition is followed by hypertrophy. Overwork—that is, work beyond the nutrition and muscular power of the organ—leads to dilatation.

These may be due to conditions *intracardiac* or *extracardiac;* the former is sometimes called *cardiopathy*, the latter, when due to vascular influences, is known as *cardiac arteriopathy.*

Among the intracardiac causes are included those valvular lesions, already described, which persist sufficiently long to influence materially the amount of work that the heart is called upon to perform; these include both obstruction and insufficiency. There has also been described a form of subvalvular stenosis characterized by narrowing of the aortic area of the ventricle immediately on the cavity side of the aortic orifice; the condition is called *subvalvular* or *pre-aortic stenosis* or

subvalvular constriction.[1] In the cases reported by Shennan and Smart the condition was associated with aortic obstruction. Myocardial sclerosis is sometimes given as a cause of cardiac hypertrophy. It is probable, however, that in most, if not all, hearts in which fibroid change and hypertrophy are concurrent the sclerosis has followed the hypertrophy, and not the reverse. Overstimulation of the cardiac muscle resulting from excessive use of alcohol, tea, or tobacco is also given as one of the intracardiac causes of hypertrophy; it is presumed that the influence of these agents is manifested by overstimulation of the motor ganglia of the heart or by an inhibiting influence on the regulating mechanism of the organ.

The important extracardiac causes increasing the work of the heart are usually grouped as (1) *physiologic* and (2) *pathologic*. The physiologic include the increased work demanded in individuals performing hard labor and in athletes. Cardiac hypertrophy is usually held to be a physiologic process during gestation. There has been considerable discussion as to whether either of these factors is important in the production of cardiac enlargement; the weight of authoritative opinion seems to be in favor of according them a certain value, which, however, is not great. The most important of the pathologic causes are the arteriopathies, which increase the blood-pressure. These include narrowing or hypoplasia of the aorta, arteriosclerosis, and especially the latter when associated with chronic interstitial nephritis. Pericardial adhesions, and other forms of chronic pericarditis, necessarily increase the amount of work demanded of the heart. In addition to the foregoing, there are instances of cardiac hypertrophy occurring particularly in infants, and often congenital, for which no satisfactory explanation can be given.[2]

Hypertrophy of the left ventricle is by far the most common, but hypertrophy of the right occurs not infrequently. Those of the preceding causes that may here act are apparent, and to such may be added: (1) Rise of pressure in the pulmonary area due to mitral disease; (2) narrowing of the pulmonary blood-vessels, as in congenital stenosis of the pulmonary artery; reduction in the vascular area of pulmonary artery, as in emphysema and interstitial pneumonia; (3) valvular lesions of the right side; (4) tumors and aneurysms pressing upon the pulmonary artery.

Morbid Anatomy of Hypertrophy.—Hypertrophy may involve the entire myocardium or may be largely restricted to the wall of a single cavity, usually the left ventricle. When the entire heart is involved, the organ is both lengthened and broadened. Hypertrophy of the auricle without dilatation rarely, if ever, occurs. When the wall of the left ventricle is involved, the apex of the heart is formed by the myocardium of that side, and is usually displaced toward the left. Hypertrophy of the right ventricle broadens the heart more than when the opposite side is involved; the lengthening is less marked. The test for hypertrophy is increased weight; hearts weighing over 1800 gm. have been reported.

[1] See Allbutt, "A System of Medicine," edited by Allbutt and Rolleston, 1909, vol. vi, p. 433. Also Shennan, "Lancet," Jan. 7, 1905, p. 21, and Smart, "Lancet," Nov. 19, 1904, p. 1417.

[2] Hedinger, "Virchow's Arch.," Bd. 178, No. 2. Simmonds, "Münch. med. Woch.," Jan. 24, 1899.

In uncomplicated hypertrophy the myocardium it often redder than in health, firm, and resists incision. Frequently there is an associated fibroid or fatty change, in which case the muscle is paler than normal; if fibroid, the density is increased; if fatty, the organ is soft. Histologically there is probably a numeric increase of muscle fibers, and, during the active stage, both the new and the old fibers are larger than normal.

Life History of Hypertrophy.—Hypertrophy is not a disease, but a definite physiologic process with the distinct object of meeting a demand for more cardiac force: just as any muscle responds to an increased stimulus for energy, the heart may respond. It is, however, imperatively necessary that the demand be not too suddenly expressed, and that abundant nutrition be supplied to attain the desired end. It will be observed that most of the causes already given are progressive in character and permanent in action, and will, therefore, indefinitely increase the demand for work; or advancing years, with the concomitant changes in general nutrition, or the inroad of other processes, such as Bright's disease, modify the nutritional value of the blood and lessen the available food-supply for the heart. In either case the compensation that nature has attempted may be overthrown by the wasting that the new changes induce. In the earlier stages of stenosis and insufficiency abundant nutrition and slowly increasing work favor the occurrence of hypertrophy, with which there may be a certain degree of dilatation. The hypertrophy, however, exceeds the dilatation; with the increased cavity there is a proportionate increase in the volume of muscle. Later, dilatation gains on the hypertrophy, compensation fails, and the circulation, possibly for the first time, begins to manifest evidences of embarrassment. Hypertrophy then passes into dilatation.

Acute dilatation,[1] may or may not be *preceded by hypertrophy.* Cases occur in which the existing nutrition can not supply a suddenly expressed demand for more than the usual work of that particular heart; ordinarily, this is met by the reserve force of the organ, but this may be deficient as the result of general malnutrition or local disease, as occurs in granular degeneration and myocarditis; or the work suddenly thrown on the heart may be beyond the capacity of the reserve force; in either case the inability of the organ fully to perform its function leads to a gradual accumulation of blood within the cavity, and dilatation results. Acute dilatation occurs in mountain climbing, after severe exertion, and sometimes during excitement; suddenly developed valvular insufficiency, as from laceration or rupture of a leaflet, may bring about the same result. The myocardium may yield and the cavities overdistend under the influence of bacterial toxins. This form of acute dilatation is especially observed in diphtheria, pneumonia, rheumatic fever, typhoid, influenza, and other infectious diseases characterized by intense toxemia. In some of these conditions (diphtheria) the dilatation develops with such rapidity as to cause practically instantaneous death. Occasionally the myocardial weakness comes on somewhat insidiously and may appear during convalescence; Clifford Allbutt has particularly called attention to this form of cardiac overdistention following typhoid fever. In patients exhausted

[1] De la Camp, "Zeit. f. klin. Med.," vol. 51, Nos. 1 and 2. Stanley, "Brit. Med. Jour.," Dec. 26, 1903, p. 1636. Menninger, "Arch. Schiffs- und Tropen Hyg.," Nov., 1903. Dawe and Austin, "Lancet," 1904, vol. ii, p. 496.

by protracted illness, such as tuberculosis, or profound blood dyscrasiæ, —for example, chlorosis, pernicious anemia, and leukemia,—a moderate acute or subacute dilatation may result from slight exertion.

Chronic dilatation, as previously mentioned, usually follows hypertrophy, when compensation can no longer be maintained.

Morbid Anatomy of Dilatation.—Most common on the right side, and most marked in all the cavities in aortic incompetency. The auricle never hypertrophies without dilatation, and may attain an enormous size. Dilatation of a cavity leads to dilatation of the orifices that communicate with it, and hence to incompetency. Opacity of the endocardium has been noted. The muscle-fibers not uncommonly show advanced degenerative change, and in some cases a well-defined interstitial myocarditis may be present. Degeneration of the cardiac ganglia has been observed.

Influence of Cardiac Failure on the Circulation and Nutrition of Other Organs.—Lesions of the valves or orifices, and alterations in the texture of the myocardium, may render the heart unable adequately to propel the blood onward, in which case accumulation in the venous system, distention of capillaries within organs, chronic congestion, malnutrition, edema, pigmentation, and other conditions follow. In order to appreciate the extent of the alterations depending upon cardiac inefficiency it is necessary to consider, briefly, the sequence of events resulting from disease affecting the aortic orifice; for present purposes it is immaterial whether the lesion of the orifice be obstruction or regurgitation. In either case the increased work thrown upon the left ventricle will, in favorable cases, be met by hypertrophy, which, under the advancing lesion, becomes inadequate, the myocardium yields, and dilatation results. When the distention of the left ventricle reaches a certain point, the valves of the mitral orifice, if not already involved, become insufficient because of the increased size of the opening—relative insufficiency. This condition results in a recoil of blood into the left auricle during each contraction of the dilated ventricle. The auricle now receives the normal quota of blood coming from the pulmonary veins, and also that regurgitating through the mitral orifice. This leads to dilatation of the auricle, which may, in favorable cases, be accompanied by slight hypertrophy. The relatively thin wall of the auricle is not equal to any continued stress, and, therefore, the hypertrophy is rarely, if ever, marked. In the meantime the pulmonary veins—the orifices of which are not guarded by valves—encounter the blood recoil resulting from the relative insufficiency of the mitral; the increasing resistance due to progressing inefficiency of the left side more and more influences the pulmonary circulation, first by raising the tension of the pulmonary veins followed by extension into the capillaries, and eventually the pulmonary arteries. For the first time the right side of the heart encounters increased tension in the pulmonary area, and must therefore increase its capacity for work or yield and dilate. Under favorable conditions the wall of the right ventricle hypertrophies, raises the pulmonary tension sufficiently to assure delivery of the requisite amount of blood into the left ventricle, and in so doing subjects the pulmonary capillaries to the deleterious influence of persistently increased tension. Failing nutrition, and continued demand for force beyond the capacity of the myocardium of the right wall, lead to its failure,

very much in the same way as on the left side. The resulting dilatation of the right cavity causes the tricuspid valves to become inefficient regurgitation occurs, and the tension in the systemic veins rises.

In the meantime the congested lungs suffer from the baneful influences of a flagging circulation. The connective tissue and elastica[1] increase, here and there areas of circulatory stasis appear, and the erythrocytes, under the influence of hemolysis, disintegrate and yield their altered pigment to the pulmonary parenchyma. The indifferently nourished bronchial mucosa becomes progressively more and more susceptible to infections, and hence chronic bronchial inflammation, often slight but usually persistent, finds a permanent abode in these structures. The pigmentation gives rise to a brownish color, the increase in interstitial tissue, and the bronchial thickening, render the lungs firmer than in health, the resulting condition being known as **brown induration.** The sputum contains leukocytes and epithelial cells in which the altered pigment is often present in abundance. While the condition, just described, has been progressing in the lung, important structural changes have been taking place in other organs. Failure in normal progression through the right ventricle necessarily causes a rise of tension in the larger venous trunks, and this in turn is transmitted to the capillaries of the organs drained. The increased capillary tension is attended by changes similar to those already described as occurring in the lung. In the liver the dilated and distended capillaries increase the size of the organ, the hemolytic processes induce pigmentation, the indifferent nutrition and accumulation of irritants are followed by connective-tissue hyperplasia (**cirrhosis of congestion**), and degenerative, necrotic, or atrophic changes give rise to wasting of the parenchyma cells (**red atrophy**); all of these combine to render the hepatic function less efficient than in health. As the capillary pressure within the liver rises, the portal blood encounters increased resistance within the hepatic capillaries and the consequent tension is transmitted to the venules and capillaries, the confluent branches of which form the portal vein. The congested spleen increases in size, the connective-tissue content of the organ rises, splenic hemolysis increases, and pigmentation of the parenchyma progresses. Such spleens are frequently the site of infarction. Similar influences are manifested, through the gastric and intestinal veins, on the capillaries of the intra-abdominal alimentary canal, deleteriously influencing the nutrition of the intestinal mucous membrane, consequently lessening its secretory and absorbing functions, and thereby interfering with digestion and attacking nutrition at a vital point.

While the tissues drained by the portal circulation are undergoing the changes just described, the increased venous tension has given rise to important alterations in the kidney. Under the influence of the rise in venous pressure, and consequent capillary slowing, these organs develop changes similar to those that have been described in the lung, liver, and spleen. The renal epithelium is ill-nourished, the connective tissue proliferates, the consistence of the organ is increased, and the condition called **cyanotic induration** is gradually produced. The fluid output from such organs may not, at first, be altered materially; usually the urine is increased in quantity. Sooner or later, however, the kidneys become unequal to the task of secreting the toxic substances con-

[1] Pearce, "Proc. of the Path. Soc. of Phila.," July, 1901, p. 215.

tained in the blood, and consequently these bodies accumulate in the circulating fluid.

Cardiac Edema.—The rise of venous tension impedes the circulation in the extremities, particularly the legs, alters the endothelium of the capillaries, and eventually gives rise to edema. This same tendency results from the heightened pressure in the portal circulation inducing the **ascites** from which these patients commonly suffer. Transudates within the thoracic serous cavities (**hydrothorax** and **hydropericardium**) may occur. With this wide-spread circulatory disturbance general nutrition suffers, the muscles waste, the ability to combat infections is lessened, and the patient falls a prey to some minor infection, pulmonary edema and infarction, uremia, or other legitimate consequence of the circulatory inadequacy.

BLOOD-VESSELS.[1]

ARTERIES.

The normal artery is composed of: (*1*) *Tunica adventitia*, or areolar sheath of fibrous tissue. (*2*) *Tunica media;* (*a*) in the larger blood-vessels this consists of elastica and resilient fibrous tissues with but little muscle-fiber; (*b*) in the arterioles the involuntary fibers predominate and but little of the elastic tissue is present. (*3*) *Tunica intima* is histologically identical with the endocardium, and is known as the endangium; it lines the interior of all the blood-vessels and constitutes the wall of the capillary.

Arteritis.—Inflammations of the artery may involve the external coat and contiguous tissues—*periarteritis;* the internal coat—*endarteritis;* or the middle coat—*mesarteritis.* Many of the conditions ordinarily described as inflammatory and grouped under the term arteritis are composite processes, partly degenerative and partly inflammatory. In other instances inflammatory lesions may precede degeneration or degeneration may occur in the cellular accumulation resulting from past inflammatory processes.

I. Atheromatous Arteritis.—(Synonyms, *Endarteritis Chronica Nodosa*, *Endarteritis Deformans.*) The artificial production of atheroma by adrenalin is usually construed as supporting the contention that the disease is due to hypertension. The affection is seen particularly in connection with conditions in which, at some time or another, a rise in arterial pressure occurs. It is not certain, however, but that the poisons giving rise to the hypertension may also induce degenerative and necrotic lesions in the elastica, which is always involved. This form of arteritis has been thought to be due to primary sclerosis of the vasa vasorum. The condition is frequently associated with chronic interstitial nephritis, syphilis, gout, and rheumatism. Overeating, alcoholic intemperance, protracted mental stress, and excessive sexual indulgence are accepted as causes. The disease is rare, but not unknown, in the young; its occurrence increases with advancing years and it is almost invariably present in adults who have passed the half century mark. The disease appears earlier and progresses farther in men than in women.

[1] The important literature on diseases of the arteries may be found in, or traced from, article by Coplin, "Proceed. of Path. Soc. of Phila.," 1904, n. s., vol. vii No. 5, p. 133.

Morbid Anatomy.—Atheroma involves particularly the larger vessels, and especially the arch and the thoracic and abdominal aorta, in the order given. All of the larger branches of the arterial tree may be affected. The abdominal branches and the arteries of the lower limbs are usually more susceptible than the subclavian and its branches. The vertebral and larger arteries at the base of the brain are not infrequently affected. It is particularly prone to occur around smaller branches given off by larger trunks; at such points it gives rise to elevated rings surrounding the lumen of the afferent vessel, the sectional area of which is diminished. By reducing the blood-carrying capacity of the involved vessels the nutrition of the organs supplied by such structures is necessarily affected. Diffuse, nodular, and linear types of the affection have been described. The first manifestation of the condition consists of a grayish or milky, semi-translucent opacity of the intima, never universal, but confined to patches here and there; this is followed by elevation of the patches,

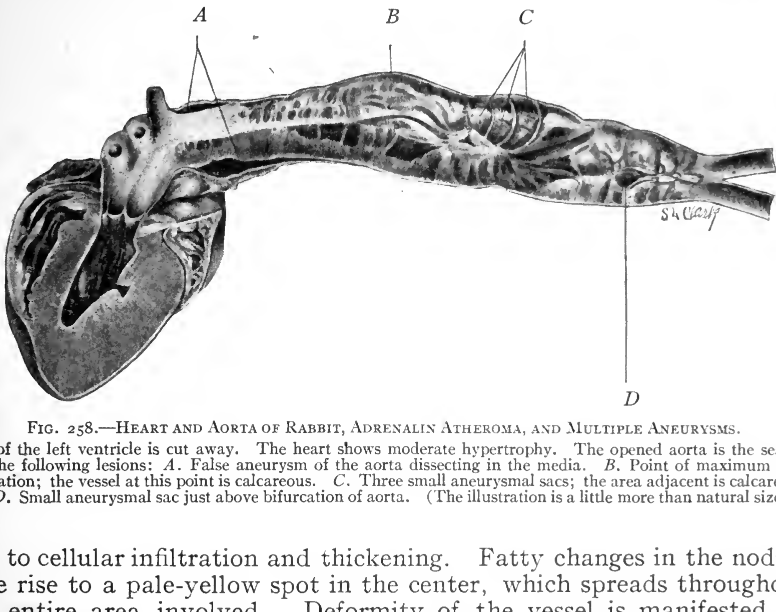


FIG. 258.—HEART AND AORTA OF RABBIT, ADRENALIN ATHEROMA, AND MULTIPLE ANEURYSMS.
Part of the left ventricle is cut away. The heart shows moderate hypertrophy. The opened aorta is the seat of the following lesions: *A*. False aneurysm of the aorta dissecting in the media. *B*. Point of maximum dilatation; the vessel at this point is calcareous. *C*. Three small aneurysmal sacs; the area adjacent is calcareous. *D*. Small aneurysmal sac just above bifurcation of aorta. (The illustration is a little more than natural size.)

due to cellular infiltration and thickening. Fatty changes in the nodule give rise to a pale-yellow spot in the center, which spreads throughout the entire area involved. Deformity of the vessel is manifested by the occurrence of button-like elevations, usually most marked where a branch is given off, and irregular dilations. The studies of Sailer and Pfahler[1] indicate that the vessels are elongated as well as dilated. A central necrosis in the atheromatous areas, with more or less fatty change gives rise to liquefaction. This may terminate by involving the intima, which exfoliates, leaving an irregular, so-called atheromatous ulcer; or fibroid and calcareous changes, rarely the former, with absorption of the liquefied part of the mass, may perpetuate the condition as a fibrous or calcific area, corresponding in size to that of the primary infiltration and subsequent necrosis. Histologically the first change which I have been able to detect is fragmentation of the elastica with some

[1] "Amer. Jour. of Med. Sci.," Oct., 1903, p. 616.

swelling between the fibers, promptly followed by the accumulation of mononuclear cells in which necrotic and degenerative changes give rise to liquefaction. The process terminating in the formation of a small cavity containing liquid is usually referred to as a degeneration, and is regarded by some observers as a form of fatty metamorphosis. I am convinced that it is a necrosis, but the distinction is not a matter of practical importance. The degeneration commences near the media. The new tissue disintegrates, forming a small cavity filled with granular debris, oil globules, and occasionally cholesterin. Degeneration may spread to and invade the media, although extensive involvement of this stratum is not common. The cellular infiltration of the arterial wall may be first manifest or most marked around the branches of the vasa vasorum.

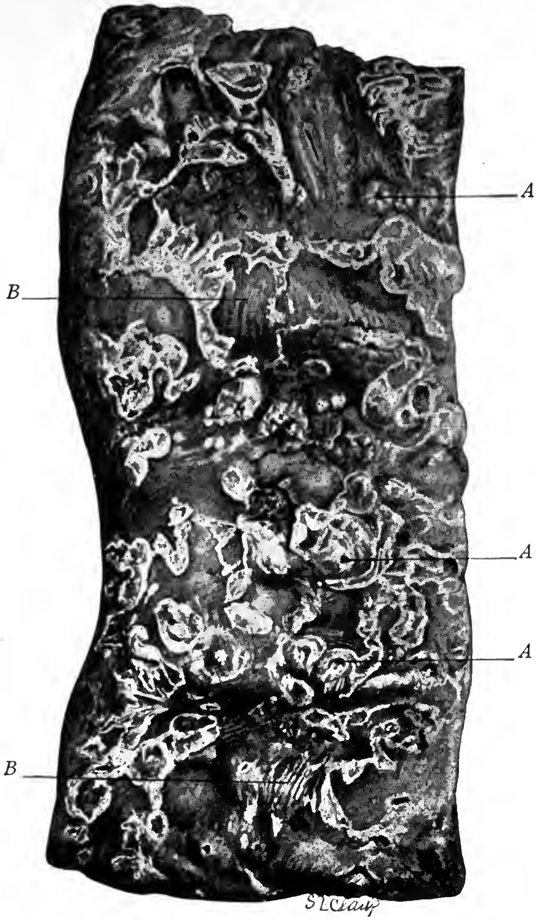


FIG. 259.—AORTA, OPENED, SHOWING DIFFERENT TYPES OF ATHEROMA.

The surface is most extensively altered by infiltration, degeneration, and necrosis. Many of the necrotic areas are calcified and could be fractured by bending. *A*, *A*, *A*. Elevated obstructing patches of atheroma surrounding exit points of small branches. *B*, *B*. Linear atheroma.

Atheroma gives rise to loss of elasticity, weakening of the wall, and increased liability to aneurysm. The arterial tube being made rigid, the cardiac work is thought to be increased, although upon this point authorities are not fully agreed.

II. Arteritis obliterans[1] is observed in association with tertiary syphilis and contracting kidney, and is present, as a local process, in the vessels supplying areas of tuberculosis. Obliterative changes are physiologic in the vessels of the fetus which become

[1] Bradford and Lawrence, "Jour. of Path. and Bact.," May, 1898, p. 195. Gould, "Lancet," March 15, 1902. Morgan, "Jour. Amer. Med. Assoc.," Nov. 29, 1902, p. 1359. Branson, "Path. Soc. of London," Dec. 6, 1904. Whitacre, "N. Y. Med. Jour.," Jan. 28, 1905.

useless at birth, and in the arterial supply to the parturient uterus, after labor. A similar, but not identical process occurs in the branches of ligated vessels, especially those not participating in the production of any succeeding collateral anastomosis.

Morbid Anatomy.—The disease is primarily an affection of the smaller vessels, but may extend centripetally, producing thrombosis in the larger trunks. The affected vessels are hard, often cord-like, usually smooth externally, although the obliterating process is rarely symmetric internally. Histologically the condition is characterized by extensive endothelial proliferation which gradually encroaches upon the lumen and

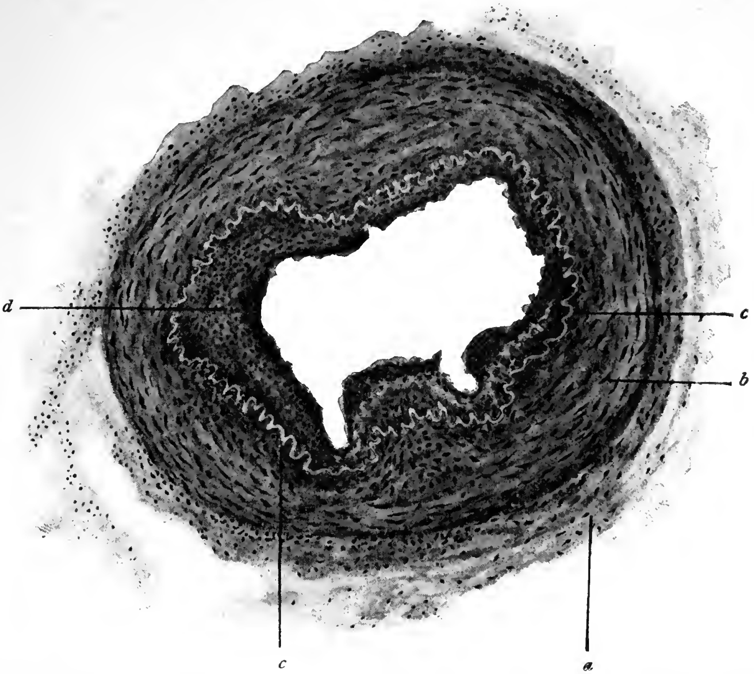


FIG. 260.—OBLITERATIVE ENDARTERITIS.—(*The tissue from which drawing was made was removed from near a cancer of the face, and prepared in the laboratory of the Jefferson Medical College Hospital by Dr. Thomas Leidy Rhoads.*) 1-inch objective, 1-inch ocular.

Specimen fixed in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin, and mounted in balsam. *a.* Adventitia. *b.* Media. *c, c.* Elastic lamina. *d.* Irregularly thickened intima. The gross specimen was hard, cord-like, but not nodular.

at the same time greatly thickens the vessel wall. It is not believed that the final obliteration of the vessel results from a progressive hyperplasia of the intima, but that thrombus formation is constantly present and sometimes completes the closing of the vascular lumen. In specimens that I have examined there was rarely any conspicuous alteration in the elastica. In some cases the internal elastic lamina is reduplicated, but this I have often observed independently of vascular disease. The absence of changes in the elastica and the fact that degeneration and necrosis appear never to involve the newly formed tissue constitute

the conspicuous differences between this affection and arteriosclerosis and atheroma.

The obliterative change gives rise to ischemia, which may be progressive and sometimes terminates in gangrene. In the case reported by Morgan gangrene occurred in the four extremities and necessitated amputation of both legs and one hand. In the case reported by Branson all the palpable peripheral arteries were indurated; one renal artery was involved and the kidney supplied by the vessel was shrunken. The figures accompanying Bradford's[1] report of a case of endarteritis of the renal arteries strongly resemble the condition under consideration. The reporter, however, does not call it an instance of obliterative endarteritis; the interlobular arteries were thrombosed and the cortex of the kidney necrotic. This form of arteritis may be associated with Reynaud's disease. The cause of the obliterative change is unknown; it is sometimes associated with syphilis, but clearly all cases are not of syphilitic origin.

III. Arteritis infectiosa[2] properly embraces all of the infectious diseases that may involve the arteries. It is customary, however, not to include tuberculosis and syphilis in the group, but to apply the name to the more acute inflammations due to infectious agents. The condition is practically always of bacterial origin, and Gilbert and Lion have shown that it may be produced experimentally by bacterial toxins. As an affection beginning on the intima it is nearly always the accompaniment of some condition attended by the presence of bacteria in the circulating blood. In such cases it is not certain whether the infection results from mural implantation, or bacterial embolism of the vasa vasorum. The condition is of frequent occurrence in pyemia and may be associated with ulcerative endocarditis. Thayer has especially studied its occurrence in typhoid fever, and it is known to be present occasionally in pneumonia, influenza, puerperal fever, and other infectious diseases, including gonorrhea. Guyot maintains that the rheumatic, gouty, diabetic, and even the arteriosclerotic endarteritides are really of infectious origin. In other cases the affected vessels are involved as a result of periarterial disease, such as abscess and other suppurative conditions contiguous to the arteries.

Morbid Anatomy.—In the *mural variety* of infectious arteritis the initial lesion is in the intima, the endothelium of which roughens, followed by implantation of platelets and a deposit of fibrin. This rapidly converts the lesion into a thrombo-arteritis, and the subsequent manifestations are those of thrombosis and embolism.[3] The *interstitial variety* may be due to extension of the mural form, infection of the media by the vasa vasorum, or involvement of the vessel wall from the exterior. In these cases leukocytic infiltration is often marked and softening of the vessel may lead to rupture or to the development of an aneurysm. When infection involves the artery by extension from a contiguous tissue the resulting lesion is called *secondary arteritis*, and partakes of the essential features of the inflammatory process which caused it.

[1] "Jour. of Path. and Bact.," May, 1898, p. 195.

[2] Holst, "Norsk Magazin for Laegevidenskaben," April, 1901. Coplin, "Proceed. of Path. Soc. of Phila.," May, 1904, p. 133. Witte, "Zieg. Beitr.," 1905, Bd. 37, H. 1. Guyot, "L'Arthritis, Maladie generale, Microbienne et Transmissible," 2 ed., Paris, 1905. Allbutt, "Lancet," July 18, 1903, p. 139. Thayer, "Bull. of Johns Hopkins Hospital," Oct., 1904.

[3] See pp. 270 and 278; also examine Fig. 146, p. 274.

IV. Endarteritis Verrucosa, *or Warty Endarteritis*, is a rare condition, and probably results from the organization of thrombi on the wall of the vessel; it usually affects the larger vessels—the aorta or the iliac or femoral arteries.

Morbid Anatomy.—Smooth warty growth on the interior of the vessel, the same color as the intima, and projecting into the lumen. The mass is at first composed of young cell elements, and later, for the most part, of fibrous tissue covered by endothelium.

V. Periarteritis Simplex was described by Charcot as a characteristic lesion of the small arteries of the brain leading to hemorrhage. The recent studies of Ellis[1] show that the changes are not distinguishable from those observed in arteriosclerosis, and that the disease is not, therefore, a morbid entity. The miliary dilatations formed are all false aneurysms, in which appropriate sections disclose rupture of the intima and blood dissecting between the coats of the vessel.

VI. Arteritis Nodosa.[2]—This condition has been described as occurring in the vessels of the heart (coronary artery), stomach, kidney, spleen, and muscles. The exact cause is not known, but an infective origin is probable. As a rule, the smaller vessels alone are involved. Macroscopically, the irregular nodular enlargements vary in size from 1 or 2 mm. in the smaller vessels to 0.5 cm. in the larger. It has been thought that the affection did not involve the blood-vessels of the brain, but recent studies by Schrötter[3] would indicate that the cerebral vessels may be affected. The vessels are dilated in some areas, and at other points contracted. An abundant cellular infiltration occurs in the outer coat of the vessel; the media degenerates; the intima may manifest proliferative changes. The small sac-like dilatations not uncommonly contain clots.

VII. An endarteritis cartilaginosa[4] has been described. The lesion is obliterative in character and affects particularly the intracranial arteries. The intima and media may be slightly infiltrated by mononuclear cells; the conspicuous change, however, is the encroachment upon the lumen by tissue consisting of a hyaline matrix in which are cells indistinguishable from those of cartilage—some resembling chondroblasts—and associated with the presence of more or less fibrous tissue.

Arteriosclerosis.[5]—Under the name arteriosclerosis have been considered a number of conditions, either associated or occurring independently. Many writers on the subject have grouped the lesions already described, and, by reason of the fact that they are occasionally associated, assumed that they were but different expressions of a general process. Gull and Sutton apparently intended to restrict the process to changes

[1] Ellis, "Proc. Path. Soc. of Phila," 1909.
[2] Beitzke, "Virchow's Archiv.," Feb., 1910.
[3] "Wiener klin. Wochen.," April 15, 1899.
[4] Marburg, "Centralbl. f. allgem. Path. u. path. Anat.," 1902, Bd. xiii.
[5] Coplin, "Proc. Path. Soc. of Phila.," May, 1904, n. s., vol. vii, p. 133. Josué, "La Presse Méd.," May 4, 1904, p. 281. Furst, "Wien. med. Presse," Dec. 18, 1904. Ribbert, "Centralbl. f. allgem. Path. u. path. Anat.," Dec. 31, 1904, p. 993. Savill, "Trans. Path. Soc. of London," 1904, vol. lv, p. 375. Rzentkowski, "Berl. klin. Woch.," 1904, No. 31. Prym, "Virchow's Arch.," 1904, Bd. 177, p. 485. Jores, "Virchow's Arch.," 1904, Bd. 178, p. 367. Ehlers, "Virchow's Arch.," 1904, Bd. 178, p. 427. Sawada, "Deut. med. Woch.," 1904, p. 425 Dunin, "Zeit. f. klin. Med.," 1904, lvi, Nos. 5 and 6.

in the capillary and arteriole walls associated with an increase in fibrous tissue; to this condition they gave the name of *arteriocapillary fibrosis*. As the clinical studies of the affection were extended, it was observed that atheroma, periarteritis simplex, etc., were not infrequently associated with changes in the arterioles and capillaries. This led to grouping all these conditions under the one term—arteriosclerosis. Thoma concluded from his studies of the process that it was not to be restricted to the arteries, but that it involved the whole circulatory apparatus, and hence he termed the condition *angiosclerosis*. Having considered the changes observed in atheroma, arteritis obliterans, and the forms of periarteritis, an idea may be formed as to what is meant by arteriosclerosis. In the clinical sense, some assume that all of the foregoing are but different manifestations of the same process.

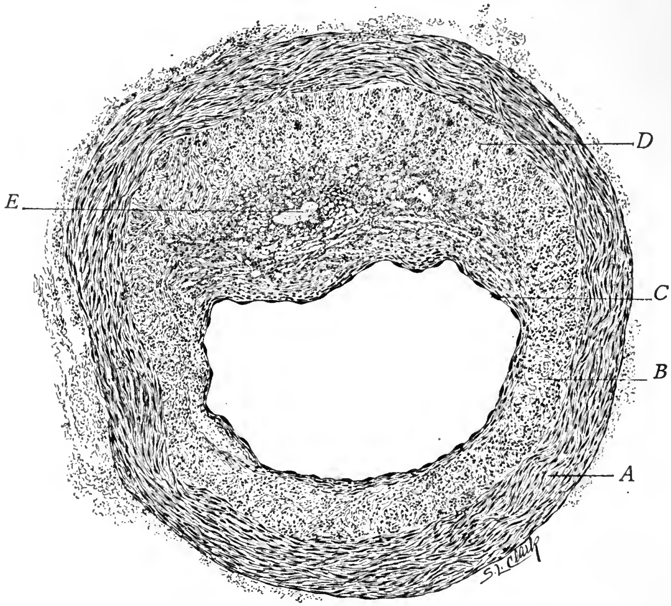


FIG. 261.—CORONARY ARTERY, SHOWING ARTERIAL SCLEROSIS.
A. Adventitia. *B*. Media. *C*. Intima. *D*. Degenerating newly formed tissue which at *E* shows advanced softening.

Old age is said to be one of the causes; the presence in the blood of the poisons of gout and rheumatism, and of the irritant bodies, whatever they may be, which induce chronic interstitial inflammation of the kidney are important factors. The excessive use of nitrogenous food, the abuse of alcohol, poisoning by lead (chronic form), and the poison of syphilis are active causes.

That atheroma, obliterative changes, and arterial degenerations are largely due to increase in the blood-pressure is indicated by the fact that under normal conditions the pulmonary artery is rarely involved, but in mitral stenosis, with increased intravascular tension in the lung and marked rise in the blood-pressure of the pulmonary artery, the vessel not infrequently shows atheroma; and in cases in which the right ven-

tricle hypertrophies, and thereby further raises the pressure, atheroma may be widely distributed in the pulmonary artery and its branches. Exactly what raises the blood-pressure of the left side is not always easily determined. The method by which it is raised is, of course, more readily comprehended. Thus, if it be assumed that the heart increases

FIG. 262.—ARTERY, EARLY STAGE OF ARTERIOSCLEROSIS.

Stained especially for the demonstration of the elastica; Weigert's method, followed by Mayer's carmalum and picroindulin. *A*. Broken and curled elastica which at places shows fragmentation. *B*. Fibrohyaline thickening of the intima; within this stratum can be seen short crinkled fragments of elastica that have been regarded by some authors as efforts at regeneration. Fragmentation of the elastic lamina is particularly marked just above the leader from letter *B*. The media in this vessel appears much broader than normal, but it is most difficult, if not impossible, to say that it is hypertrophied.

FIG. 263.—ARTERY, ARTERIOSCLEROSIS.

Stained especially for the demonstration of the elastica; Weigert's method, followed by carmalum and picroindulin. *A*. Fragmented and separated elastica. B. Fragmented and curled elastica; note the swelling of the isolated fragment and the curled end at *B*. *C*. Unusually crinkled elastica resulting from yielding and recoil due to solution in continuity at *A* and *B*. *D*. From just below the leader from *D* to upper part of drawing there is no break in the elastica. It will be observed that in that part of the vessel still possessing a practically normal elastica there is no thickening of the intima and subintimal stratum, while the area of altered elastica is overlaid by a fibrohyaline newly formed tissue containing bits of elastic tissue. There is some fragmentation of the external elastic lamina which is present in this specimen but absent from the arteries from which Figs. 262 and 264 were made.

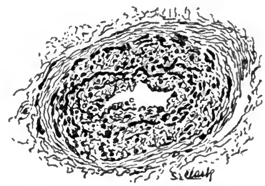


FIG. 264.—ARTERY, ADVANCED ARTERIOSCLEROSIS.

Stained especially for the demonstration of the elastica; Weigert's method, followed by carmalum and picroindulin. In this specimen little more than irregular fragments of the elastic lamina are present. The endothelium no longer forms a separate layer, but, as the result of proliferative changes, the inner stratum is composed of young connective-tissue cells. There may be some doubt as to whether this vessel, during life, transmitted blood.

its output of blood into the aorta, and at the same time there is no yielding in the arterioles throughout the body, the arterial tension must rise. On the other hand, if the heart continue its normal output, and there be contraction of the arterioles, a similar rise in pressure must be brought about. That heightened tension has something to do with the

evolution of arteriosclerosis is indicated by possible experimental production in animals of lesions resembling those observed in this form of arterial disease in man. (See Fig. 258, p. 521.) Dunin has found that in fully developed clinical arteriosclerosis the blood-pressure may be below normal; prior to the occurrence of degenerative changes in the myocardium the tension is usually above the normal, and when interstitial nephritis is present the arterial pressure is frequently extremely high, sometimes reaching 250 mm. of mercury.

Morbid Anatomy.—In describing arteriosclerosis it may be assumed that if atheroma be properly a part of the affection, which I am inclined to doubt, it is a late manifestation. My own observations, and they are supported by the studies of Jores, have led to the conviction that the initial change is in the elastica, particularly of the smaller arterioles. In the earliest stage the internal elastic lamina is, at points, broken, and often distinct intervals can be observed between the ends of severed fibers. In such areas edema and mononuclear infiltration quickly appear, followed by the formation of new connective tissue intercalated between the elastic lamina and the endothelium of the vessel. Later the fragmentation of the elastica becomes still more marked and the encroachment upon the vessel lumen by the newly formed tissue progressively advances. In the young proliferate and in the area occupied by the normal elastic lamina there appear innumerable fine fibrils which elect the elastica stain; these are evidently of recent production, and, while others speak with confidence of their origin, I can not say with certainty whether they are formed from the new cells or from the pre-existing elastica. Analogy would justify the assumption that the latter explanation is the correct one. The different changes in the elastica are represented in figures 262, 263, and 264. This somewhat immature fibrous tissue matrix, containing the irregularly distributed elastica, evidently constitutes the hyalofibrous tissue recognized by Gull and Sutton as present in the walls of the arterioles. The encroachment on the lumen of the vessel lessens the sectional area and diminishes the amount of blood which it is able to transmit; this results in starvation of the tissue beyond. Savill has strongly urged that there is a demonstrable increase in the muscle of the affected vessel, and clinical phenomena (angina pectoris, arteriosclerotic colic, intermittent claudication) indicate that sclerotic arterioles may be spasmodically contracted. I believe it was first suggested by Hippolyte Martin that atheroma might depend upon arteriosclerotic changes in the vasa vasorum, and possibly this is the case.

The Influence of Arteriosclerosis on the Nutrition of Organs.[1]—The weight of the brain is diminished, the nerve cells degenerated, the vessels tortuous, and in some cases miliary aneurysms are present; degenerative changes have been described in the ganglion cells of the cortex. In the spinal cord, perivascular sclerosis, which is usually slight, and degenerative changes in the motor cells have been observed Interstitial fibroid change in the peripheral nerves, associated with sclerosis of the nutrient vessels, has been described. I have already referred to myocardial changes produced by sclerosis of the coronary arteries.[2]

[1] For changes in the nervous system, see Spiller, "Proc. Path. Soc. of Phila.," May, 1904, p. 156. Changes in the gastro-intestinal tract, see Longcope, ibid., p. 165.

[2] See Chronic Interstitial or Sclerotic Myocarditis, p. 495.

An arteriosclerotic cirrhosis of the liver has been described, but it is probable that the fibroid liver and vascular changes are coincident and due to the same cause, and that the hepatic induration is not the result of the vascular lesion. Opie's studies indicate that there may be some connection between arteriosclerosis and chronic changes in the pancreas, and the frequent association of diabetes, pancreatic disease, and sclerotic vessels supports this view. It has been suggested that gastric ulcer may be of arteriosclerotic origin. A form of intestinal colic has been attributed to sclerosis of the mesenteric vessels. The most important visceral lesion accompanying arteriosclerosis occurs in the kidney This condition will be considered later.[1]

Tuberculosis[2] of the arteries is rarely, probably never, a primary affection. It usually results from extension of a tuberculous process from some contiguous tissue, commonly a caseous lymph-node, in which case the arterial wall is gradually infiltrated from without, eventually giving rise to a cellular accumulation on the intima in which the histologic structure of tuberculosis can readily be recognized. By infection from the blood-stream multiple nodules of **endarteritis tuberculosa** may be produced. These may consist of minute granulations or even warty growths of some size, and are usually accompanied by miliary tuberculosis, of which they are not necessarily the cause. The endarterial caseous nodules produced by the infiltrating tuberculosis are almost invariably followed by the eruption of acute miliary tubercles in the organs.

Syphilis[3] of the vascular system has been made to include practically all forms of arterial disease. The poison of lues is generally accredited with ability to produce almost any of the chronic arterial inflammations and degenerations. Atheroma and arteriosclerosis are common manifestations of tertiary syphilis. Hübner described an **endarteritis luetica** characterized by the formation of fibrous tissue in the intimal and subintimal layer, which, by progressive narrowing, might occlude the affected vessel. In the nodular form of this affection the resemblance of the endarterial proliferate to gumma may be striking. Baumgarten studied a similar process affecting the adventitia, involving the vasa vasorum and thereby infiltrating the media; the new tissue partook of the characters usually observed in gummata. In the cerebral arteries, less frequently elsewhere, a distinct **gummatous arteritis** sometimes occurs. Clinically the influence of syphilis in the production of aneurysm is commonly recognized. The poison of syphilis induces structural changes in the elastica, lessens the resilience of the vessels, and predisposes to dilatation and rupture. To such forms of syphilitic disease of the blood-vessels Mott would apply the term **ectasial arteritis.**

Calcification[4] of blood-vessels occurs (1) as a result of atheromatous

[1] See Chronic Interstitial Nephritis.

[2] See foot-note, p. 154. Also consult Blumer, "Amer. Jour. of Med. Sci.," 1899, vol. cxvii. Bernard and Salomon, "Revue de Méd.," 1905, No. 1, p. 45. Witte, "Beitr. z. allg. Path. u. path. Anat.," 1904, Bd. 36, p. 192. Thorel, "Lubarsch and Ostertag's Ergebnisse d. allg. Path. u. path. Anat.," Neunter Jahrg. I. Abt. 1903 p. 1039.

[3] Fahr, "Virchow's Arch.," 1904, Bd. 177, p. 508. Düring, "Deut. med. Woch.," Dec. 15, 1904. Abramow, "Virchow's Arch.," 1904, Bd. 178, p. 406. Thorel, "Lubarsch and Ostertag's Ergebnisse d. allg. Path. u. path. Anat.," Neunter Jahrg. I. Abt. 1903, p. 1042.

[4] Monckberg, "Virchow's Arch.," 1903, Bd. 171. Vanzetti, "Giornale della R. Accad. di Med. di Torino," July and Aug., 1903.

endarteritis or other inflammation of the vessel; (2) when lime salts are deposited in the vascular wall, without any discernible antecedent disease, the condition is called *cryptogenic calcification.*

Ossification, or true bone formation, is said by Orth to be a possibility; exactly what induces it, or how it may be brought about, is not known.

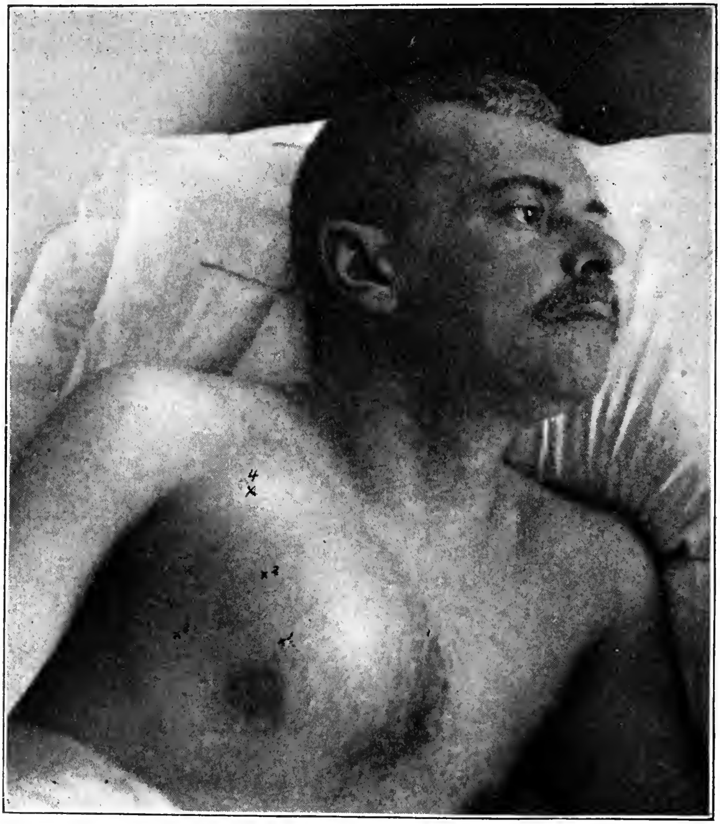


FIG. 265.—THORACIC ANEURYSM.

1, 2, 3, Points at which an inserted trocar failed to reveal the presence of fluid blood. At 4 fluid blood was found. At the autopsy a globular aneurysm 17.5 cm. in diameter was found. The sac bulged between the first and fifth ribs, the second, third and fourth ribs having been absorbed in front of it. The sac was lined by a laminated clot, 5 cm. thick, internal to which was a coagulum, 7 cm. in thickness. The aneurysm communicated with the arch of the aorta, and had been treated by wiring. (For the use of this illustration I am indebted to Dr. W. W. Johnston, Washington, D. C., who reported the case in "American Medicine," May 11, 1901, vol. i.)

Hyaline, vitreous, or **diaphanous degeneration,** allied to that form of degeneration described by Zenker as occurring in the muscles, has been found in the vessel-walls, usually in the arterioles. (See p. 247.)

Amyloid infiltration has been considered when dealing with lardaceous disease. (See p. 227.)

Fatty degeneration of the **blood-vessels** is a disease of the capillaries.

the small arteries, and, rarely, the veins. It occurs most commonly in the capillaries of the brain. As to cause, it is observed in connection with (1) old age, (2) pernicious anemia, (3) phosphorus-poisoning, and (4) general debilitating conditions. The change in the intima resembles the degenerative lesion of atheroma, but is not accompanied by any fibrous tissue formation or other phenomena so constantly associated with atheroma. The vessel-walls are converted into a fatty cellular debris without any preceding inflammatory process like that of atheroma.

An **aneurysm** is a tumor-like sac, containing blood and communicating with an artery. (See Fig. 232, p. 464.)

The *sac* may be composed of one or more coats of the blood-vessel, when it is known as a *true aneurysm* or *arterial ectasia;* when the limiting membrane of the cavity is formed by the condensed tissues around the vessel, the wall of which has entirely given way, the condition is spoken of as a *false aneurysm.*

Causes of Aneurysm.—Aneurysms are said to be (1) *traumatic* or (2) *idiopathic.* As nothing occurs without a cause, it would be better to call the latter *cryptogenic.* Further, the causes of aneurysm are said to be (1) *predisposing* and (2) *exciting.* Of the former, many of the degenerations of the vessel-walls that have been studied, and that weaken the artery, are eminently predisposing; atheroma is doubly dangerous in that it renders the vessel rigid and at the same time weakens the wall. The fact that syphilis favors or often brings about arterial disease or degeneration makes it a predisposing, if not truly an exciting, cause of aneurysm. Between the thirtieth and fortieth years of life the degenerative arterial changes described in the preceding pages are likely first to evince themselves; the heart is yet in full power, in most individuals, and, with the maintained cardiac force and diminished strength of the diseased arterial wall, rupture or dilatation of the blood-vessel is likely to ensue. Suddenly developed, powerful cardiac force—such as may occur from a hard lift, sudden spring, or vault—doubles the demand on the semi-rigid and weakened vessel-walls, and may induce rupture of one or more of the arterial coats. The male is more liable to these sudden exertions, and hence aneurysm is much more prevalent in that sex. Injury to the blood-vessel may be an exciting cause or a predisposing element; if the injury be a puncture, it may be followed immediately by a false aneurysm; a contusion may give rise to arterial changes that weaken the wall and cause it to yield when subjected to a strain that would not influence the normal vessel. Stretching and twisting of vessels, as in dislocations and fractures, or in their reduction, have been followed immediately by aneurysmal dilatation. Histologic studies of aneurysmal vessels in man, and examination of arteries in which experimental aneurysms have been produced, constantly disclose alterations in the elastica. The changes may be structural and manifested by fragmentation or larger breaks in the elastic strata; it is possible that breaks in the elastica are preceded by chemic alteration, and that the latter may, without structural change, permit dilatation. Schwyzer affirms that alterations in the collagenous tissues of the arterial wall are important factors in the production of aneurysm. It is probable that in the aneurysms due to acute infective lesions of the vessels both elastic and fibrous tissues are involved.

Form of Aneurysm.—(*A*) *Classified by the shape:* (1) *Cylindric*, uniform distention of the vessel. (2) *Fusiform*, or spindle-shaped. (3) *A cirsoid aneurysm* consists of a number of arteries irregularly dilated and lengthened throughout a considerable part of their courses. When a single artery is involved, the term *aneurysmal varix* has been applied; the same name is also used for arterio-venous aneurysm and should be suppressed. Arterial varix is better. (4) *Saccular*, in which

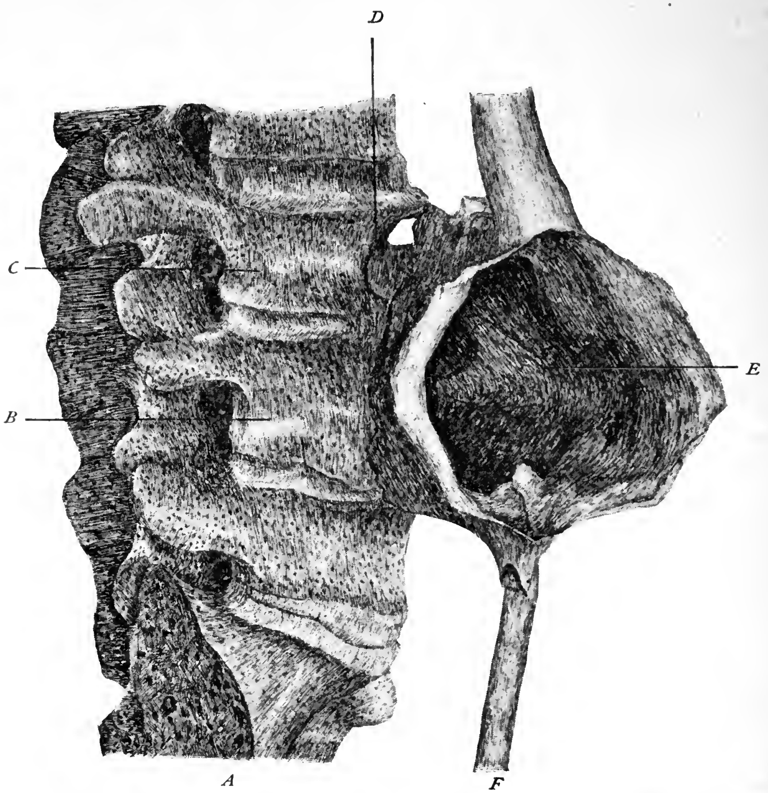


FIG. 266.—SYMMETRIC ANEURYSM OF THE ABDOMINAL AORTA.—(*Specimen in the museum of the Jefferson Medical College.*)

A. Sacrum. *B*. Fourth lumbar vertebra; the anterior part of the body has been eroded by the aneurysm. At the inferior margin calcareous material has been thrown out anteriorly; this covers the cartilage. *C*. Body of third lumbar vertebra. At *D* the aneurysmal sac has been cut away to show the absorption of the body of the vertebra. *E*. Cavity of the aneurysm. At the lower part of the cavity, between the points of exit of the two iliac arteries, a sharp spicule of a calcareous plaque will be seen projecting upward. *F*. Left iliac artery; the right iliac artery will be seen as a short stump at the lower part o t e aneurysmal wall.

a distinct pouch is formed. If on one side of the vessel and communicating by a small opening, it is spoken of as *asymmetric;* if the sac be uniformly distributed around the vessel, as in the miliary aneurysm of the brain, it is *symmetric*. (5) *Arteriovenous aneurysm* results from any injury which establishes a communication between an artery and a vein. When the wall sharply defines the aneurysm, it is spoken of as *circumscribed;* when the blood cavity terminates in infiltrated tissue,

the term *diffuse* is applied; the latter is necessarily a false aneurysm. When small and multiple, particularly in the brain, they are called *miliary aneurysms.*

(*B*) *Classified by the cause:* (1) *Traumatic aneurysm.* An aneurysm arising suddenly, as from an ulcerative endarteritis or trauma, is sometimes spoken of as an *acute aneurysm;* (2) *idiopathic* or *cryptogenic;* (3) *embolic*, due to proximal distention in occluded vessels, usually terminal; (4) *dissecting aneurysm* due to blood dissecting between the layers or coats of a vessel's wall; (5) *verminous aneurysm*, one containing a parasite such as is found in the mesentery of the horse.

(*C*) *Classification based on duration and changes in the wall:* (1) An *acute aneurysm* or *recent aneurysm* is one quickly developed, and is usually traumatic; (2) *chronic* or *old aneurysm*, an aneurysm that has persisted longer, as shown by the changes that its walls have undergone.

Results of Aneurysm.—(1) Disturbance of blood distribution; (2) pressure on surrounding tissues and organs; (3) rupture; (4) cure and arrest of further circulation through the altered vessel.

Cure of Aneurysm.—The first step in the spontaneous obliteration of an aneurysm is the formation of a clot or fibrinous deposit in the cavity; this may be in layers (laminated) (see Fig. 232, p. 464), or it may be a central clot apparently formed as one mass. By occluding the point of exit the circulation is arrested. The coagulum may remain practically unaltered for years. The writer saw a case in which all symptoms except the presence of the tumor had been absent for eight years, the proximal and distal ends of the vessel having undergone obliterative arteritis. In time, blood-vessels may permeate the clot and organization of the mass may ensue. Occasionally some of the young blood-vessels dilate and are converted into channels transmitting blood from the proximal to the distal parts of the vessel, and thereby re-establishing the circulation. (See Canalization of a Thrombus, Fig. 148, p. 276.) Organization of a clot formed within an aneurysm terminates in the production of a mass of fibrous tissue, which contracts, and often perpetuates the contour of the cured aneurysm. Above and below the healed sac, the artery involved is occluded by obliterative changes extending to the first branch through which the blood continues to flow.

Hypertrophy of Arteries.—When a large arterial trunk is obstructed, the blood-supply to the part beyond may be maintained by enlargement of branches, rising above the point of obstruction, and anastomosing with branches from below; the latter may also increase in size. The condition is one apparently of true hypertrophy. The anastomotic circulation eventually becomes as competent to carry on the functions of nutrition as were the normal vessels. When this occurs, it is said that a collateral circulation has been established by anastomosis.

VEINS.

Normal Structure.—Normal veins possess essentially the same structure as arteries, except that the tunica media is very much less developed, and hence the walls are thinner. Many of the veins are supplied with valves, and thus differ from the arteries.

Bennett[1] and others have described **congenital sacculations** and **cystic dilatation of the veins** occurring independently of, or associated with, varicosity. Such abnormalities may involve a part or all of the wall and hence may be symmetric or asymmetric. The veins of the neck and inguinal regions, and the saphena veins, may be affected; the condition is sometimes called **congenital varix.**

Phlebitis,[2] Inflammation of Veins.—Inflammatory processes analogous to those already described as occurring in the arteries (see p. 520) take place in the veins, the most important of which are the infective forms—**infectious phlebitis.** As the current in the veins is from the smaller lumen to a larger one, dislodgment occurs, and emboli are thrown off in large numbers. When considering thrombosis and embolism, this point was mentioned. (See p. 275.) The source of the infection in veins may be by (1) direct infection, as in wounds; (2) mural implantation; (3) continuity of spread (that is, passing directly along the vessel-wall); (4) by contiguity, from periphlebitis. As examples of the last two may be cited the spread from infected uterine sinuses to pelvic veins, and the extension of suppurative mastoid disease to the adjacent intracranial sinuses, respectively. Pyemia and other forms of bacteremia are frequently due to phlebitis; the latter may be secondary to the blood infection.

When the inflammation begins in the intima, as a result of extension along the wall, a thrombus usually attends the progress of the inflammation, justifying the term **thrombophlebitis.** The presence of bacteria in practically all these thrombi is usually admitted; in many of them pyogenic organisms are almost exclusively the cause, and such venous inflammation has received the name **suppurative phlebitis.** In other cases neither suppuration, softening, disintegration, fragmentation, nor dislodgment occurs. The absence of such changes indicates that the condition is not suppurative, but by no means excludes infection, such as typhoid fever, influenza, and, as shown more recently, rheumatism. The simple, bland, or **noninfective phlebitis,** such as follows injury of the vein without infection, is inconsequential, and is usually unattended by secondary processes. In some cases the patient may suffer repeated attacks, constituting what is called **recurrent phlebitis.**

The results of phlebitis are influenced by the character of the accompanying infection, and especially by the changes occurring in the resulting thrombus. The latter I have considered when dealing with thrombosis (p. 275). When the inflammation is attended by the formation of an occluding thrombus, the affected vein is frequently obliterated. Osler[3] has been able to collect twenty-nine instances of thrombosis involving the superior vena cava; to these should be added the instance

[1] "Lancet," April 12, 1889, p. 788.

[2] See references to Thrombus, p. 270. Also Censier, "Revue de Méd.," vol. xxii. Pinatelle, "Gaz. Hebdom. de Méd.," Dec. 19, 1901. Oettinger, "La Semaine Méd.," Feb. 12, 1902. Terriberry, "Med. News," April 12, 1902. Hess, "Deut. med. Woch.," June 26, 1902, XXVIII Jahrg. Ducastel, Thèse de Paris, 1903. Chantemesse, "Acad. de Méd.," July 28, 1903. Aldrich, "N. Y. Med. Jour.," March 5, 1904, p. 442. Heller, "Berl. klin. Woch.," June 9, 1904, No. 23. Galtier and Pierre, "Gaz. des Hôp. Civil. et Mil.," Sept. 3, 1904. Ledderhose, "Deut. med. Woch.," Oct. 20, 1904. Cobbledick, "Practitioner," Nov., 1904, p. 707. Förster, "Wien. klin. Woch.," Nov. 3, 1904, p. 1175. Halbron, "La Presse Méd.," March 18, 1905, p. 173. Letullè, "Soc. de Biol.," April 8, 1905.

[3] "Bull. of Johns Hopkins Hospital," July, 1903.

reported by Cobbledick. The circulation in the area drained by the occluded vessel is more or less impeded, the nutrition of the structures disturbed, and edema is frequently present.

Tuberculosis of the veins is manifested by changes essentially similar to those already described (see p. 529) as occurring in the arteries, but is much more frequent. The paths of infection in the two kinds of vessels are essentially similar, and the dangers from dissemination of the bacilli by the blood are practically identical.[1]

Syphilis of the veins may be of the sclerotic or gummatous type. Nodular syphilitic phlebitis gives rise to circumscribed enlargement (gummata) along the course of the affected vein. In other cases the induration is cord-like and not nodular.

Chronic phlebitis or **phlebosclerosis** is a morbid entity studied by Thoma, who believes it to be part of general vascular disease (*angiosclerosis*). The wall of the vein, usually immediately beneath the intima, shows a marked increase in the fibrous tissue, which may undergo hyaline degeneration; the elastica is commonly affected as in arteriosclerosis and thrombosis is not infrequently present.

FIG. 267.—VARICOSE VEINS OF THE LEG.—(*Gould.*)

Varicose Veins, or Phlebectasia[2] (Synonyms, *Varix, Varicosity*).—This condition consists of more or less irregular dilatation of the veins; as a rule, associated with alterations in their walls and nutritive changes in the area involved.

Sites.—Veins of the leg and thigh; plexus pampiniformis; hemorrhoidal veins; occasionally, the veins of the abdominal wall, and, rarely, intra-abdominal veins—peri-uterine, renal, or mesenteric.

Causes.—Dilated veins may result from (1) obstruction to the onward flow of the blood: *e. g.*, tumors of the pelvis, pregnancy, etc., inducing varicosity of the veins of the leg and of the rectum; cirrhosis of the liver, obstructing the veins returning from the alimentary canal; tight garters or other constricting bands are also causes. (2) Diseases of the central organ of circulation, leading to venous stasis. (3) Pulmonary obstruction, inducing stagnation of the blood in the veins. (4) Inflammation of the veins, (*a*) leading to softening of the walls, and thus favoring expansion, and (*b*) obliteration or narrowing of a large vein, such as the femoral, by a thrombus or by contraction, thereby increasing the intravenous pressure in the vessel, distal to the point of obstruction. Bennett believes there is always a congenital defect, in the presence of which other conditions may produce varicosity; he also regards many cases as congenital.

Forms.—(1) When the dilatation is regular, symmetric, and not associated with lengthening, the condition is known as *simple dilatation;* (2) when the vein is dilated and tortuous, owing to apparent lengthening as well as to dilatation, it is spoken of as *cirsoid dilatation;* (3) when

[1] See Tuberculosis, p. 154.

[2] Thorel, "Lubarsch and Ostertag's Ergebnisse d. allgem. Path. u. path. Anat.," Neunter Jahr. I. Abt., 1903, p. 113. Ledderhose, "Deut. med. Woch.," Oct. 20, 1904. Bennett, "Lancet," Nov. 22, 1902, p. 1374.

the distention is irregular, saccular, or upon alternate sides, the condition is called *varicose dilatation.* (4) An *ampullary dilatation* of the veins has also been described; this form occurs particularly near the femoral ring and has been mistaken for hernia. By some writers the congenital sacculations and cystic dilatations, referred to on page 534, are placed in this group.

Results of Phlebectasia.—The slowed circulation and passive congestion lessen the nutrition of the tissues in the area drained by the involved vessels; as a result of failure to remove effete materials, degenerative or even necrotic processes may ensue. Edema may occur; clots may form in the veins; the stretching of the walls usually renders the valves inefficient; as a result of the lowered vitality, slight bruises or superficial excoriations are followed by infection in the diseased area, and extensive ulceration commonly ensues. In the testicle lessened nutrition undoubtedly results, and in some instances this may be followed by atrophy of the organ. In the rectum, clotting may occur in the dilated hemorrhoidal veins, and violent inflammatory processes may follow, or the venous mass may ulcerate and bleed, or may, by its size, cause more or less obstruction to the passage of fecal matter.

Tumors of Blood-vessels.—Primary tumors of the blood-vessels are rare. They must be of the connective-tissue series. Sarcomata invade the vessels rapidly, and particularly the veins, by which they not uncommonly spread. Cancers can implicate the vessels only as secondary growths or by direct extension of the neoplasm into the vessel-wall. (For tumors of the blood-vessels, blood-vessel tumors, see Hemangiomata, p. 345.)

LYMPH-VESSELS.

Nutrition of the tissues is largely maintained by the lymph, which is derived from the blood, and circulates in the interstices or primitive lymph-spaces. (See Edema, p. 267.) It is generally believed that, primarily, the lymph is free in the reticulum between the cells, the cavities within which it is lodged being called the *primitive lymph-spaces.* From these structures there arise the lymph capillaries, which join to form the lymphatic vessels. The larger lymph-vessels possess walls structurally resembling the walls of blood-vessels. The lymphatic capillaries, or lymph canaliculi, are structurally like the blood capillaries, except that they show great irregularity in diameter, often exhibiting saccular, cylindric, and fusiform dilatations.

Malformations of the lymph-vessels are usually manifested as congenital tumors (*lymphangiomata*), which have been considered elsewhere. (See p. 346.) As in the blood-vessels anomalies of origin and course are occasionally observed, so in the lymphatic vessels evidences of abnormal distribution of the channels are sometimes exhibited. Thus, carcinoma of the mamma, which usually first invades the axillary nodes, may show initial glandular involvement in the supraclavicular nodes, thereby proving that, in some instances, at least, the lymph stream from the breast passes in a direction at variance with the normal.

Obstruction of a lymph-vessel may result from pressure, as when adjacent tumors, aneurysms, and cicatrices collapse its walls; injury, inflammation, thrombosis, tuberculosis, and animal parasites (such, for

example, as the filaria, see p. 207) may also occlude its lumen, or excision of lymph-nodes, extensive suppurative processes, and lymphangeiolitis may destroy the ducts traversing an area. Cancer spreading by the lymphatics may plug the vessels. The changes resulting from occlusion of a lymph-vessel depend largely upon the importance of the vessel and upon the possibility of collateral anastomoses. The distribution of the lymphatic system commonly affords abundant opportunity for the lymph to pass through some circuitous route when obstructed in its normal course. When passage in this way can not be provided, the resulting obstruction is associated with edema in the area involved. (See Edema, p. 267.) In other cases, either with or without edema, the lymphatic vessels distal to the obstruction dilate. The dilatation may be restricted to a small area, in which case a lymphangioma results, or it may be diffuse, and manifested by the occurrence of small cysts in the tissue involved. In still other instances, either with or without any of the foregoing conditions, more or less edema, with marked proliferation of the connective tissues, occurs, giving rise to **elephantiasis** (see p. 209) and **elephantoid conditions** (see p. 210). Manson's statistics show that in 96.84 per cent. of the cases of elephantiasis the lower extremities are involved; in 5.86 per cent. the upper extremities; and in 2.3 per cent. the scrotum manifests the change. The enormous overgrowth of the connective tissues may be appreciated by the fact that the scrotum sometimes attains a weight of 200 pounds. On incision, the tissue involved is found to consist largely of white fibrous elements superficially, and deeper, of a "blubbery-looking dropsical tissue." The lymphatic nodes of the area involved are commonly enlarged and fibrous.

Occlusion of the thoracic duct affords a slightly different picture by reason of the fact that the vessel transmits chyle. It may be obstructed from the same causes as those already given for lymphatic trunks elsewhere. Thrombosis involving the left innominate vein occludes the duct at the point where it empties its contents into the venous circulation. As in obstruction of other lymph-channels, it is possible to have occlusion of the thoracic duct without any untoward manifestation, in which case the fluid that it normally transmits must enter the circulation through some circuitous route. As a result of obstruction, **chylous ascites** may occur. (See p. 454.) Similar effusions are occasionally observed in the pleural cavities, and **chylocele**—an accumulation in the tunica vaginalis testis—at times follows obstruction to the course of the intra-abdominal lymph. In other cases there is an accumulation of chyle in the lymphatics of the scrotum, constituting so-called **lymph-scrotum**; and in still other instances the obstruction to the onward flow of the lymph is manifested by the occurrence of **chyluria.**

As a result of obstruction to the flow of the chyle along its normal course in the vessels of the mesentery, cysts are occasionally formed. Not infrequently **chyle-cysts**[1] closely resemble abscesses, for which they have been mistaken. A microscopic or chemic examination of their contents prevents this error in diagnosis. Obstruction to the onward flow of chyle materially interferes with nutrition, leading to more or less anemia, and eventually, in many cases, to emaciation.

[1]See reference, p. 480. Also Mériel, "Revue de Chir.," Dec. 10, 1903, p. 736

Lymphangitis, angioleucitis, or inflammation of the lymphatic vessels occurs in two forms—*acute* and *chronic*.

The acute form is usually due to infection by pyogenic organisms, and is, therefore, commonly suppurative in character. It may accompany erysipelas or may result from the extension of infections, such as abscesses. The dissection and postmortem wounds, of common occurrence and great mortality before the proper injection of anatomic material, were typical examples of **acute suppurative lymphangitis.** That acute inflammation of the lymphatic vessels is not always the result of infection is indicated by the occurrence of a typical form due to filaria, and of another variety, brought about by the introduction of venom into the lymph-spaces. Severe bruises and burns, the former often without any solution in the continuity of the skin, may be followed by acute lymphangitis.

The morbid anatomy of the condition depends largely upon whether the process is restricted to the lymph-spaces or passes beyond these structures and invades the vessel properly so called. In the former instances (**acute reticular lymphangitis**) there is dilatation of the blood-vessels, giving rise to redness, which often shows a peculiar mottling due to its irregular distribution. More or less edema (swelling) is present. In the **acute tubular lymphangitis** the lines of hyperemia and swelling follow the course of the lymphatic vessels; usually they are broader than the duct, as a result of the presence of an associated **perilymphangitis,** or, rather, a reticular lymphangitis surrounding the inflamed vessel. On microscopic examination, the lymph-spaces will be found to contain numerous leukocytes, and later, in pyogenic infection, the accumulation may be sufficient to justify its being called a distinct pus collection. Fibrin is nearly always present at some stage in the process. In the lymphatic vessels swelling and desquamation of the endothelium occur, associated with more or less marked leukocytic migration, and not infrequently with thrombosis. The extent and termination depend largely upon the character of the infection and upon the resistance of the individual. In areas of lymphatic obstruction—such as lymph-scrotum and elephantiasis—the absence of sufficient protective powers on the part of the tissues may lead to disastrous infections. In other cases the virulence of the infecting agent may be overwhelming, and associated with the production of poisons that rapidly destroy life, or by the diffusion of bacteria into the lymphatic nodes, and eventually into the blood-vessels, septicemia or pyemia may ensue. In still other instances the virulence of the infection may be slight or the resistance of the tissues marked, and in either case the process quickly subsides.

Chronic lymphangitis may follow the acute form or may result from gradually developing obstruction to the onward flow of lymph. It is frequently observed in lymphangiomata. It is manifested by more or less dense edema of the area involved, with proliferation of the connective tissue, leading to a true fibrous induration.

Lymphangiectasis and lymphangioma have been referred to in considering tumors. (See p. 346.) Tumors of the lymph-vessels, aside from those resulting from lymphangiectasis, either congenital or acquired, are usually secondary, and are due to invasion of the adjacent tissues or primitive lymph-spaces. *Endotheliomata* of the serous membranes are usually regarded as primary tumors arising from the endo-

thelium, and are allied to, if not identical with, similar tumors the origin of which is the endothelium of smaller lymph-spaces or lymph-ducts. The extension of cancer by the lymph-spaces has already been considered. (See p. 323.)

In connection with or independent of associated tuberculosis of the lymph-nodes the process may involve the vessels. Extension onward to the nearest nodes or to the blood-stream is possible. When tuberculosis occurs in the thoracic duct[1]—either as a result of mural implantation of tubercle bacilli, which have found entrance near the periphery of its distribution, or when an adjacent tuberculosis invades the structure—disaster due to systemic dissemination is prone to follow.

[1] See Longcope; reference given on p. 154.

CHAPTER VII.

MUCOUS MEMBRANES.

Normal Structure.—A mucous membrane consists essentially of three parts: (1) Upon the surface, a layer of epithelial cells; (2) a basement membrane, upon which these cells rest; (3) the submucous connective tissue, in which ramify the blood-vessels, lymphatics, and nerves essential to the life and function of the layers above.

1. The *epithelial layer* varies in two particulars: (*a*) in the character of the epithelium and (*b*) in the number of layers. When the function of the epithelium is largely protective, stratification is the rule; when secretion is the essential function, there is commonly but one layer: *e. g.*, on the tongue numerous layers are found, while in the tubules of the stomach, the acini of glands, and the secreting structures of the kidney, etc., but a single stratum exists. When, in addition to protection, propulsive force is needed, or when the latter alone is demanded, the epithelial cells are supplied with cilia, as in the bronchi and Fallopian tubes. In all mucous membranes possessing stratified epithelium there lies immediately adjacent to the basement membrane a genetic layer analogous to the cylindric-cell layer of the rete mucosum of the skin. When the epithelial covering is simple (nonstratified), as in the pulmonary vesicles and renal tubules, a distinct genetic layer may not be demonstrable. Mucous membranes so constructed must, after exfoliation or destruction of a single layer, resurface the connective-tissue basement membrane from the viable cells at the margin of the area involved, exactly as epithelial regeneration progresses over the surface of an ulcer undergoing repair.

Epithelial cells possess the remarkable faculty of manufacturing from supplied nutrition new chemic compounds not existing, as such, in the pabulum supplied: *e. g.*, the secretions of the salivary glands, the gastric follicles, the pancreas, the kidney, etc. Every mucous surface is, therefore, a laboratory, and this peculiarity has given the membrane the name specialized, indicating that it possesses characters eminently its own. While all mucous membranes elaborate something, the most constant element is mucus; when a mucosa is altered by disease, mucus not uncommonly forms a conspicuous product in the altered secretion; as a rule, the greater the functional perversion, the more abundant the abnormal products, and the larger the quantity of mucus. As the function of the epithelial cell is dependent largely upon the pabulum supplied, and as this supply is controlled by the subepithelial layers, it becomes evident that the alteration of the basement membrane, or of the submucosa, must affect the activity of the superimposed epithelium.

2. *The Basement Membrane* (*Membrana propria*).—This structure is mesoblastic in origin, composed of fibrous tissue and, in some situations, a scant supply of unstriped muscle-cells, and a varying quantity of

elastica. The thickness of the basement membrane varies greatly; thus, in the mouth and nose it is of a discernible thickness, while in the wall of the pulmonary alveoli it is demonstrated with difficulty. When great changes in the volume and surface of the organ are likely to occur, the basement membrane may be thrown up in irregular ridges; in this way the gastric mucosa is enabled to adapt itself to the changes in volume constantly manifested by the stomach. By some it is claimed that nerves and lymphatics penetrate the membrana propria and present themselves immediately in the epithelial layer. It is not, however, probable that such is the case; as in all mucosæ the basement membrane is the line between the connective and epithelial tissues, it seems reasonable to assume that it is merely pushed as a thin layer ahead of the nerve-fibers, and that the lymphatics open, if at all, immediately beneath or into the genetic layer of epithelium when such a structure exists.

3. The *submucosa*, or submucous connective-tissue layer, is of the greatest importance, and varies more than either of the preceding. In a part of the nasal fossæ it is erectile; where an organ is subject to great alteration in surface, like the stomach, it is especially abundant; where it is not called upon for such rapid alterations in surface during brief intervals, it may be wanting, as in the uterus, where it is extremely scanty, if at all present. As the nutrition of the epithelium is largely dependent upon the condition of the submucosa, lesions of this layer influence the function and structure of the overlying membrane. Many mucous membranes possess lymphoid tissue, and, in some locations, collections of *lymphoid follicles* constitute a distinguishing feature. For the most part these nodes occupy the submucosa, although in numerous situations the membrana propria contains a quantity of lymphoid tissue. The lymphoid elements may be somewhat diffuse, agminated in nodules, or grouped in patches. Lymphoid tissue, among other functions, clearly possesses antitoxic, bacteriolytic, and possibly other properties which, in the present state of our knowledge, remain undetermined. In certain infectious processes, affecting the mucous membranes,—for example, typhoid fever—the most conspicuous lesion involves, to the greatest degree, the lymphoid elements of the mucous membrane.

Hyperemia of a mucosa may be physiologic; an increased blood-supply is sent to the stomach during gastric digestion; the uterine mucosa is supplied with an excess of blood during menstruation. Pathologic hyperemia is usually a manifestation of irritation and is commonly observed as a precursor of inflammation. The blood admitted to the submucosa is increased by temperature variations and the presence of poisons of strengths inadequate to produce inflammation; it is possible that vasomotor influences may, in other ways, increase the amount of blood supplied to a mucous membrane. The form of pathologic hyperemia associated with inflammation of the mucosæ will be dealt with when considering that subject.

Congestion of a mucous surface is dependent upon conditions that interfere with the exit of blood from the affected mucosa. Congestion is seen in the lungs and upper air-passages and in the alimentary canal, as a result of cardiac disease associated with interference in the onward flow of the blood, and in the stomach and intestinal mucous membranes

in obstructive hepatic disease as well. It may or may not be the precursor of inflammation, and its permanency is dependent upon the condition that causes it.[1]

The function of the membrane is materially altered by the faulty metabolism that always attends a stagnant circulation. In time an increase in the fibrous tissue of the submucosa occurs, usually preceded, accompanied, and followed by a catarrhal process manifested in the overlying epithelial layers. In obstructive diseases of the lungs or heart the congestion of the gastric mucous membrane may be so great as to resemble the lesions resulting from poisoning. The venous stasis sometimes gives rise to hemorrhage which may be recurring and, although usually slight, occasionally is severe. If congestion be prolonged, varicosity of the submucous veins frequently develops; rupture of such varices may give rise to alarming or even fatal bleeding

Hemorrhage from the mucous membrane occurs as a physiologic process in menstruation; hyperemia and congestion not uncommonly terminate in hemorrhage, as in yellow fever, malaria, and allied conditions. It is not always an evidence of a serious malady, as is shown by the occurrence of trifling epistaxis without apparent cause. In hemophilia and scurvy, epistaxis is frequently present. As to severity, a hemorrhage may consist of the trifling escape of a few red corpuscles in an abundant mucous exudate (serosanguineous) or it may be alarming; the escaped blood may pour out on the surface as in epistaxis, or it may infiltrate the submucosa (interstitial or purpuric hemorrhage) and be found postmortem in the intestines or elsewhere as petechiæ, ecchymoses, or larger collections in the submucosa. During life, in purpura, exposed or visible mucous surfaces may exhibit the discolorations in a typical manner. These spots, if large, may, in very exceptional cases, terminate in necrosis, and, if the patient survive, ulcers may develop, although this is rare; as a rule, if recovery occur, the blood is absorbed without any septic or gangrenous process.

Atrophy of the mucous membrane may be an insidious process, due to malnutrition and the action of toxic substances, or to inflammation and sclerosis of the submucosa; the epithelium is principally affected.

Hypertrophy of the mucous membrane, in the sense that there is a notable increase in the functional activity, is not known to occur. In a number of conditions the thickness of the submucosa is conspicuously increased and occasionally the epithelial layer is thickened; as a rule, these changes are due to irritation or inflammation and are not accompanied by any augmentation in the specific function of the affected membrane; usually physiologic activity is lessened or suppressed.

INFILTRATION OF THE MUCOUS MEMBRANES.[2]

Pigmentary Infiltration.—(A) **Pneumoconiosis,** or pulmonary pigmentation due to extraneous substances, assumes a number of forms. Solid particles may gain ingress to or through the mucous membrane from the surface, as in laborers whose occupation exposes them to the constant inhalation of suspended solid matters: *e. g.*, the inhalation of coal-dust by miners leads to a condition in the lungs known as **anthracosis**; in the grinders of metal instruments, in nailers, etc., iron inhaled

[1]See p. 265. [2]See pp. 231 to 234.

gives rise to an allied condition, known as **siderosis** (when the disease occurs in nailers, it is also known as *nailer's phthisis*); in stone-cutters and the makers of grindstones, etc., the disease is known as **lithosis** or **chalicosis.** Similar infiltrations occur in laborers in cotton and shoddy mills and in the handlers of grain. These pigment particles do not seem to be able to penetrate the stratified epithelium, but gain ingress further down in the air-passages; the alveoli being permeable, the epithelial cells not arresting all the pigment, it enters the lymph-spaces of the basement membrane, from which the extraneous substance diffuses by the lymphatic channels into the surrounding tissues. The deposited material finds lodgment in the following structures (Hamilton): in the subpleural and interbronchial tissues; in the peribronchial lymph-nodes; in the lymphadenoid interspaces of the alveoli.

After the infiltration is well advanced in the pulmonary tissues, the substernal and general mediastinal glands are usually involved. Weigert has shown that the circulation may be reached by the pigment passing

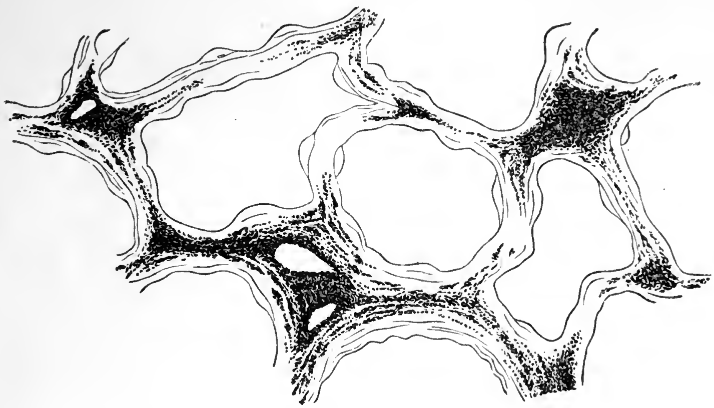


FIG. 268.—SECTION OF THE LUNG, PNEUMOCONIOSIS.—(*Rindfleisch.*)
The deposited pigment is shown in the connective tissue of the vesicular wall.

through the peribronchial nodes, which attach themselves to the pulmonary veins, into which they rupture. The presence of foreign solid material induces inflammation of the mucous covering—at first acute, but from the continued application of the irritant, the changes incident to chronic inflammation occur. In the deeper tissues fibroid hyperplasia ensues, with the abundant production of new fibrous tissue in the infiltrated areas. The accompanying catarrhal processes denude the epithelial protecting layer, and the lung tissue becomes exposed to the dangers of infection by bacteria. The introduction of pyogenic organisms induces an infective inflammation which may terminate in necrosis, and eventually give rise to cavity formation; or, what is much more common in susceptible individuals, the tubercle bacillus gains entrance to the affected tissues and tuberculosis is engrafted on the existing lesions. Aside from the lung, pigmentary infiltration is occasionally seen in the vomer and turbinated bones.

Medicometal Pigmentation of Mucosæ.—Occasionally, metallic substances taken as medicines or otherwise may be precipitated in or on the mucous membranes with which they come in contact. Examples of this are seen after the administration of iron and bismuth.

(B) Pigment Deposit from the Blood.—**Brown induration** of the lung is in part a pigmentary infiltration, secondary to chronic congestion. The disease is most marked in the lung in chronic heart disease. The alveolar epithelium contains altered blood pigment, and pigmented cells are found in the interalveolar wall. The capillaries are distended, and the fibrous tissue of the lung is increased in amount. The lungs, on opening the chest, do not immediately retract; they are at first brownish-red in color, but on exposure to the air they become livid from the oxi-

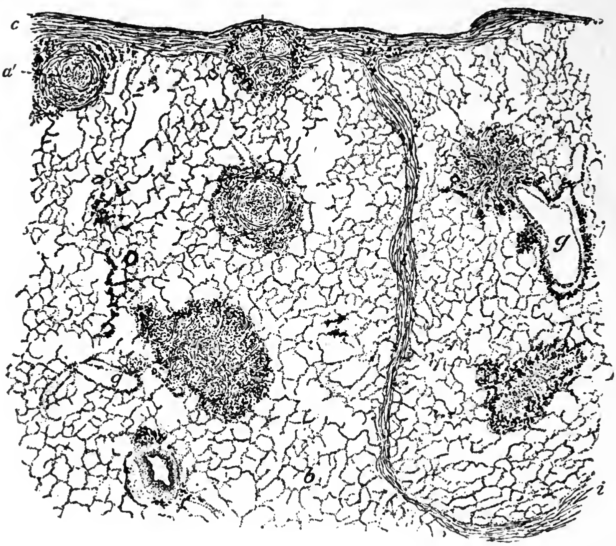


Fig. 269. Section of Lung Showing Chalicosis.—(*Schmaus.*)
a. Collection of infiltrated material lodged in the pleura, c. A capsule of fibrous tissue has formed around it. a' Similar nodule in the lung tissue. Other nodules are shown. b. Unaffected pulmonary tissue. c. Pleura g, g. Blood-vessel, around one branch of which a nodule is forming. i. Interlobular septum, showing some thickening.

dation of the excessive quantity of hemoglobin; as a result of the increase in fibrous tissue the organs are denser than normal, cutting and tearing with considerable resistance.

Deposition of coloring-matter is found in other mucous membranes, where constant or repeated congestions occur, as in malaria; the intestinal, gastric, and hepatic tissues showing the change in the highest degree.

Fatty infiltration seems exceedingly rare, if it ever occurs, in a mucous surface. The author has never seen it. It may be present in the glands of the mucosa.

Albuminoid or amyloid infiltration,[1] when the general disease is pres-

[1] See p. 227.

ent, invades the mucous membrane (submucous blood-vessels) of the stomach and intestines, rarely the gullet or the air-passages.

Calcareous infiltration is usually secondary to chronic inflammatory and necrotic changes in the submucosa.

DEGENERATIONS OF THE MUCOUS MEMBRANES.

Granular degeneration,[1] or *cloudy swelling*, occurs in the various epithelial structures as the result of infection of the mucosa or the action of bacterial toxins reaching the epithelium through the blood. The condition has also been attributed to high temperature and to various autointoxications. The affected cells are granular, the nuclei obscured, and desquamation hastened. Granular degeneration accompanies necrosis and all forms of inflammation attacking mucous membranes.

Fatty degeneration,[2] or *fatty metamorphosis*, representing, as it does, a later stage of the granular process, will be seen when the latter condition has persisted for a time with continuing or progressively increasing causes. It has been noted in pernicious anemia.

Coagulation necrosis[3] affecting mucous membranes is not materially different from the same process occurring elsewhere. It may be in-

FIG. 270.—GRANULAR DEGENERATION (CLOUDY SWELLING) OF THE LIVER CELLS.—(*Schmaus.*)

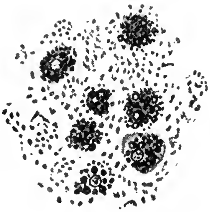


FIG. 271.—FATTY DEGENERATION OF THE LIVER CELLS.—(*Schmaus.*)

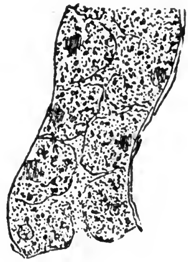


FIG. 272.—GRANULAR DEGENERATION OF THE KIDNEY EPITHELIUM (CLOUDY SWELLING)—(*Schmaus.*)

duced by chemic agents, such as lactic acid, and is sometimes due to contact with heat. A similar, but probably not identical, process results from the action of necrosing poisons, such as strong alkalies and concentrated acids The usual cause of coagulation necrosis, as observed on mucous membranes, is infection; the most typical form of the lesion is observed in mucosæ attacked by the diphtheria bacillus.[4] The typhoid ulcer is in part the result of coagulation necrosis affecting the patches of Peyer. The streptococcus, pneumococcus, and sometimes other infections give rise to this form of necrosis.

Morbid Anatomy.—On the mucosæ, particularly that of the pharynx, coagulation necrosis may be restricted to an exudate forming on the surface, constituting what is sometimes called a false membrane. In the presence of more intense irritation, as by diphtheria bacilli of rela-

[1] See p. 247. [2] See p. 242. [3] See p. 251.
[4] See p. 118 and examine Fig. 67, p. 120.

tively high virulence, the necrosis extends into the submucosa or occasionally deeper. Histologically the structure is composed of a matrix in which fibrin is often conspicuous; epithelial cells and leukocytes are commonly abundant. Where the lesion extends into the submucosa, separation of the necrotic material results in the formation of an ulcer, the size of which corresponds to the extent of the necrotic process. The condition is most frequent in the pharynx, and in pseudomembranous inflammation of the larynx, trachea, and bronchi; it also occurs in certain infections of the intestine.

INFLAMMATION OF THE MUCOUS MEMBRANES.

There is probably no tissue in the body so prone to inflammatory processes as the mucous membranes, and since these inflammations occur as the result of many and complex causes, and are modified by the character of the membrane, as well as by its function and by the cause, to describe each anatomic and etiologic form would require more time and space than is allotted to the present volume. For convenience of description the inflammations are divided into the (1) catarrhal, (2) pseudomembranous, (3) hemorrhagic, (4) gangrenous, (5) suppurative and (6) chronic infectious.

Catarrhal inflammation of the mucous membranes may be acute or chronic. The former is usually of brief duration and, unless exceptionally severe, does no irreparable damage to the affected mucosa. The chronic process is of indefinite duration, usually begins in the acute or a succession of acute attacks, or, in some cases, insidiously. If at all intense or prolonged, as is usually the case, permanent changes are produced in the tissues involved.

Acute catarrhal inflammation arises as a result of many complex causes applied from without or exerting their influence from the circulatory side of the membrane. The process is practically always a manifestation of infection, although predisposition has no little influence in determining the character, duration, and other essential phenomena of the lesions. Nearly all the acute infectious diseases—such as measles, scarlet fever, typhus fever, diphtheria, etc.—are accompanied by, or may incite, a catarrhal inflammation of one or more mucous surfaces; the same is true of the chronic infections, such as tuberculosis and syphilis, when they affect a mucous membrane.

The application of other irritants to the mucous surface is, next to infection, the most common cause, and embraces a multitude of subcauses: *e. g.*, foreign bodies; contact of the mucosa with heat, in the form of hot air, steam, or a liquid such as hot water; irritant gases, as chlorin, bromin, ammonia, sulphurous acid; poisons, such as escharotics like the mineral acids, arsenic, etc., in dilutions too weak actually to induce necrosis of the surfaces with which they come in contact. Inflammatory conditions in the mucosæ may also arise from irritants due to chemic changes in foods, whether the irritant be preformed when the food is taken or develop subsequently by fermentation or other change; as examples of these may be mentioned ptomain poisoning and gastric catarrh due to the ingestion of decomposing or fermenting foods. Alcohol is also a cause.

While rapid thermic and barometric changes and excessive humid-

ity are alleged causes, they probably act by altering the secretion or circulation, or both, thereby lessening the normal resistance to infection; it is not improbable that many of the previously given causes act in a similar manner. Pure mycoses of the mucous surfaces may incite a catarrhal inflammation, often violent in character; as an example of mycotic infection, apparently restricted to the mucous membrane, thrush is most frequently cited. Bright's disease, rheumatism, gout, and allied diseases may be causes or predisposing factors. The young and the aged, more than those in middle life, seem susceptible to diseases of the mucous membranes.

The foregoing is intended to indicate types of causes of mucous membrane inflammation, and is in no way a catalogue of the possible etiologic factors. The same cause rarely gives rise to inflammation of a number of mucosæ simultaneously, although it may possess the power to do so. It has been demonstrated that the pneumococcus may produce conjunctivitis, rhinitis, pharyngitis, tracheitis, bronchitis, and pneumonia, and also that it may attack the alimentary mucosa, endometrium, and Fallopian tubes. As a rule, however, it affects, at one time, continuous mucous membranes only. Another fact to be borne in mind in connection with catarrhal inflammations is that, no matter what the type of inflammatory lesion affecting a mucous membrane, there is practically always an associated catarrhal process. Typhoid, cholera, and dysentery frequently induce other lesions, but a catarrhal inflammation of the intestinal mucosa is essentially always present. In the pharynx and larynx, less frequently in the nose, the diphtheria bacillus is capable of producing extensive necrosis, false membrane, even hemorrhagic inflammation, but with all of these a varying degree of catarrh occurs.

Morbid Anatomy.—In acute catarrhal inflammation of any mucous membrane, it is practically always possible to recognize three stages; in the first, sometimes called the *dry stage*, or *stage of hyperemia*, the secretion is lessened; in the second, known as the *exudative stage*, the discharge from the mucosa is more abundant than normal, a peculiarity justifying the name **acute catarrh,** sometimes used for the process; the third stage, in favorable cases, constitutes the period in which regeneration and restoration to the normal occur.

In the first stage of the inflammation the surface is dry, or is lightly covered by a thick, sticky, adherent mucus; during life hyperemia is shown by the intense redness, which, in violent cases, may assume a dusky red; a little later is added evident submucous edema, due to the hyperemia and progressing exudation of serum in the submucosa. The histologic changes of this stage are engorgement of the submucous vessels and infiltration of the submucosa with serum and leukocytes; the epithelium is cloudy and swollen, and beginning desquamation is usually evident. The morbid physiology is shown in excessive dryness, giving rise, in the vocal organs, to the husky, rough voice or to a cough; in the nose, to the "stopped-up" feeling, which is intensified by the erectile tissue becoming far more distended by blood than is possible in mucosæ containing no such structure; in the stomach, the absence of secretion causes anorexia and nausea, and in the intestines, constipation.

Immediately following the first or dry stage—which may be brief

or unusually prolonged, rarely the latter—an abundant discharge from the affected mucosa occurs. The epithelial cells desquamate with the greatest rapidity, and the surface, instead of being dry and sticky, becomes flooded with mucus. The rapidly exfoliating cells undergo granular and fatty degeneration, necrosis, and desquamation with such promptness that the special secretion of the part is not elaborated: *e. g.*, in the stomach, pepsin production is arrested; in the salivary glands, there is a lessened output of digestive ferment, and the production of mucus is excessive. The mucous membrane may fail to produce, even in small quantities, the agent which normally it is the function of the mucosa to elaborate; the apepsia of gastritis may be taken as illustrating this functional inadequacy of an inflamed mucous membrane. The inflammatory discharge is composed of the debris resulting from necrosis and consequent fragmentation of the epithelium, a varying quantity of serum, epithelial cells, free nuclei, and leukocytes; more or less of the serum infiltrating the submucosa passes through the basement membrane, and may be sufficient in quantity to justify calling the inflammation *serous;* in very severe cases many red blood-corpuscles escape.

The patient is usually relieved, the submucous circulation being re-established and the perivascular exudate finding some exit by the surface and the lymphatics. If the cause be now withdrawn, the circulation gradually returns to the normal, absorption of the submucous exudate is completed, and restoration of the epithelial covering from the genetic layer of the basement membrane gradually takes place. Ulceration rarely occurs. The basement membrane is probably never destroyed by a simple catarrhal process; when such destruction results, it is most likely that, during the hyperemic stage, stasis occurred in some of the vascular twigs and by the occurrence of coagulation necrosis in the affected area, an ulcer resulted.

The restoration of the mucosa is usually complete and the return of function is satisfactory. It is generally maintained that a mucous membrane once subjected to a catarrhal disturbance is rendered more susceptible to subsequent attacks. In some cases, the cause continuing to act, the process is gradually converted into a chronic catarrh; in other instances rapidly repeated acute inflammations induce structural alterations in the mucosa and lay the foundation for a more chronic lesion.

Chronic catarrhal inflammation of a mucous membrane results from the continuance of the last stage of the acute condition or eventually persists after a succession of acute attacks. The chronic inflammations are due to causes which persist—practically always an infection—and are rendered possible by antecedent or concurrent conditions, influencing the mucosa locally or lessening the bacteriolytic and allied properties of the body-juices: *e. g.*, the slowed circulation of chronic heart disease, the vascular and blood changes of Bright's disease, gout, rheumatism, malaria, chronic alcoholism, etc., by weakening the resistance of the mucous surface, favor repeated attacks of infection or the persistence of a single attack once developed. The continued presence of nonbacterial irritants also exerts a deleterious influence on the affected tissue and impedes the processes by which infection is combated and restitution of the normal accomplished. Such influences are shown

in the chronic nasal catarrhs associated with the presence of foreign bodies; constant exposure to irritating dusts and fumes is attended by similar consequences. Repeated libations also weaken the mucous membrane.

Morbid Anatomy.—The continued infiltration of the submucosa with leukocytes and serum leads to permanent alterations in tissue. Proliferation of the fixed connective-tissue cells gives rise to fibrous tissue, which, at first, is cellular, but later the cells become less abundant and contraction occurs. These changes alter the nutrition of the submucosa, lessen its blood-supply, and exert a deleterious influence on the overlying epithelium. During the earlier stages the superabundance of the submucous inflammatory products gives the membrane an appearance of thickening, and is often spoken of as an evidence of hypertrophy,

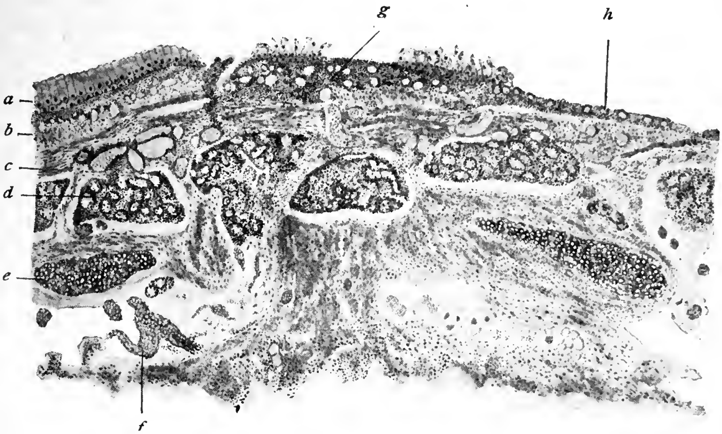


FIG. 273.—SECTION OF WALL OF BRONCHUS, CHRONIC BRONCHITIS.

Specimen hardened in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin, and mounted in balsam. (From slide prepared by Professor Harris.) *a*. Diagrammatic representation of the normal cylindric cells arranged as in health. *b*. The line runs just under the membrana propria into a mass of newly formed fibrous tissue, which extends downward to *c*. Just beyond the line from *c* are several blood-vessels distended by blood. *d*. Mucous gland surrounded by considerable fibroid thickening of the submucosa. *e*. Cartilage. *f*. Distended blood-vessel. *g*. Part of the chronically inflamed mucosa, showing inflammatory exudate and progressive fibrosis of the submucosa. The normal cylindric cells that should cover the area have desquamated, and those remaining are imperfectly formed and desquamating. To the left of the lower end of the line from *g* (1.5 cm.) is a depression which marks the exit point of a duct from one of the mucous glands. *h*. Denuded surface of the mucosa. Under this point the more recent inflammatory changes are less marked than at *g*. (¼-inch objective 1-inch ocular.)

or the inflammation is said to be *hypertrophic;* the persistent softened condition of the tube may favor dilatation in this stage. Occasionally, from obstruction of ducts, mucous glands and follicles—as in the mouth, pharynx, and trachea—become distended and conspicuous. The prominence of these structures has given to the process the name **follicular inflammation.** In other cases the lymphoid tissue is the seat of important alterations; the lymph-sinuses are distended, the endothelial cells proliferate, and an accumulation of leukocytes in the interior of the nodule occurs. As a result of these changes the lymphoid follicle enlarges and may often be recognized as a distinct, slightly indurated, or soft node in the affected mucosa. Failure on the part of the earlier observers to differentiate between the enlarged lymphoid follicles and

the distended mucous glands resulted in both processes being called follicular inflammations.

As the inflammatory process advances,—grows older,—contraction of the newly formed submucous tissue ensues, leading to lessened blood-supply to the surface and to faulty or perverted function of the mucous membrane, associated with thinning—an atrophy, giving the present stage the name *atrophic inflammation;* the absence of, or diminution in, secretion justifies the name *dry catarrh*, sometimes given to the affection. The hypertrophic and atrophic stages of the inflammation may be seen in the same subject at the same time, or the atrophy may be observed to follow the chronic inflammation without the development of very marked thickening, contraction exceeding in rapidity the process of infiltration. Whatever may have been the cause of the inflammation, the bacteria of decomposition find lodgment in the dry and slowly removed secretion, and fetid or poisonous products are developed. This is illustrated in *ozena* and in neglected chronic inflammations of the ear.

Catarrhal inflammation may occur on any mucous membrane. Of course, the accident of location gives rise to differences in the character of the lesion, but the essential phenomena will be but variations of the stages and processes indicated. The site and name for some of the accompanying catarrhal processes are as follows: Nose, *rhinitis;* mouth, *stomatitis;* tongue, *glossitis;* tonsils, *tonsillitis;* pharynx, *pharyngitis;* trachea, *trachitis* or *tracheitis;* bronchus or bronchi, *bronchitis;* in the capillary bronchi and the air vesicles, *catarrhal pneumonia* (a condition in which the catarrhal inflammation differs from that observed in other localities in the tendency to accumulation, in changes in the inflammatory products, and in other phenomena, which demand that the process be considered more in detail, as will be done when the forms of pneumonia are described); esophagus, *esophagitis;* stomach, *gastritis*, or, on account of the altered secretion and consequent symptoms of indigestion, *dyspepsia;* ileum, *ileitis;* colon, *colitis;* ileum and colon, *ileocolitis;* rectum and mucous surface of the anus, *proctitis;* urethra, *urethritis* (when due to the gonococcus and involving the urethra, the process is called *gonorrhea;* the same cause acting on other mucosæ produces what is termed *gonorrheal inflammation*); bladder, *cystitis*; ureter, *ureteritis;* pelvis of the kidney, *pyelitis;* gall-bladder, *cholecystitis;* biliary ducts, *cholangitis*. Catarrhal inflammation occurs no doubt, in the hepatic structure, but here, as in the lung and kidney, other associated phenomena require that the condition be considered separately.

Pseudomembranous, Fibrinous, Plastic, or Croupous Inflammation.—Of the many names given to this condition, the first-mentioned is preferable. The process consists of an inflammation, attended by the development, external to the membrana propria, of a false or pseudomembrane composed of a solid or semisolid matrix and entangled cell elements.

Causes.—That pseudomembranous inflammations can be induced without the intervention of bacteria is established, but that such is often the case is extremely doubtful. Heat, irritant gases, such as chlorin and ammonia, escharotics which do not destroy the basement membrane, and allied agents, may possibly give rise to inflammations attended by the development of false membrane. The local application of lactic acid and other medicaments is sometimes followed by pseudomembrane for-

mation. Of the many microbic causes, a few are established and deserve special mention. In the nose, pharynx, and air-passages the process is usually due to the diphtheria bacillus,[1] less frequently to the streptococcus,[2] and occasionally to the pneumococcus.[3] Cases of pseudomembranous inflammation have been observed in which the bacillus of Friedländer[4] was the only organism present. The pyogenic staphylococci[5] are rarely the cause. Among the less frequent organisms may be mentioned the influenza bacillus,[6] the colon bacillus,[7] typhoid bacillus,[8] and the bacillus of dysentery.[9] The ulceromembránous stomatitis or angina of Vincent[10] is sometimes attended by the formation of pseudomembrane. Investigation into the cause of pseudomembranous rhinitis, which often lasts for months, has demonstrated, in a large percentage of cases the presence of the Bacillus diphtheriæ. It would, therefore, appear that the chronic as well as the acute pseudomembranous inflammations are frequently due to the Klebs-Löffler bacillus. Pseudomembranous inflammation of the intestine has been observed in pyemia and allied septic conditions; also in pneumonia and typhoid fever, as well as in Bright's disease, cirrhosis of the liver, and cancer. A pseudomembranous bronchitis[11] sometimes accompanies pulmonary tuberculosis and occasionally arises independent of any known cause; it is probably always of bacterial origin.

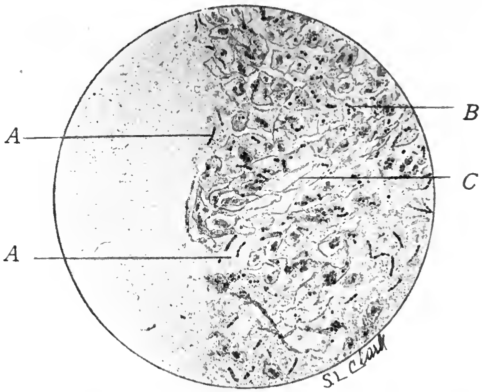


FIG. 274.—MARGIN OF PSEUDOMEMBRANE FROM TONSIL, CASE OF DIPHTHERIA

A, A. Diphtheria bacilli; the pointer from the lower *A* ends in an area of granular material. *B*. Cocci. *C*. Strands of fibrin. The cellular elements present are squamous epithelium, and polymorphonuclear and hyaline leukocytes.

Morbid Anatomy.—Two forms are recognized—an acute and a chronic; so far as known, the histology and process of development differ only in that the chronic form occupies more time. Of necessity, the process begins as a catarrhal inflammation, with hyperemia and infiltration of the submucosa; liquor sanguinis passes through the basement membrane, and, reaching the surface, the necessary ferment is supplied by the bacteria or the epithelial cells (probably the latter, as bacteria may be introduced into the circulation of an animal without immediate coagulation of the blood), and coagulation occurs. Sometimes the membrane contains a few red blood-cells, which occasionally are sufficiently numerous perceptibly to tinge the exudate; rarely hemorrhage into the membrane is conspicuous. That all pseudomembranous processes are due to the deposition of a fibrin-forming body has been strongly controverted. Wagner contended that the pseudomembrane results from a fibrinous or croupous meta-

[1] See p. 118. [2] See p. 114. [3] See p. 109. [4] See p. 127. [5] See p. 113.
[6] See p. 126. [7] See p. 136. [8] See p. 139. [9] See p. 141. [10] See p. 172.
[11] A figure illustrating this condition will be found in the article on pulmonary tuberculosis.

morphosis of the epithelium associated with degenerative changes in the cell nuclei. As Baumgarten[1] has shown, the changes described by Wagner are frequently easily detected, and it may be possible that some of the membranes are formed in the way suggested. It has also been shown that the membrane may contain mucin, and that it often fails to give the characteristic stain reaction of fibrin (p. 252). It must not be forgotten that on various mucosæ rapid alteration in the fibrin may occur, and that digestive autolytic or like changes may rob it of its specific stain reactions. The fact that mucin is present in the membrane is not astonishing when the frequent entanglement of epithelial cells containing this body is considered. Still, it must be admitted that, with the tests at our disposal, membranes apparently mucigenous and failing to give the fibrin reactions often occur; that fibrin had no part in their formation is not so easily established.

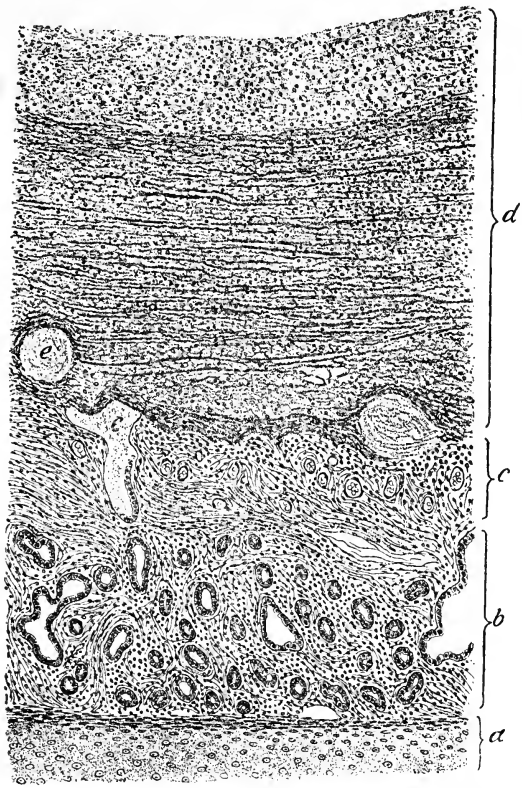


FIG. 275.—VERTICAL SECTION THROUGH THE PSEUDOMEMBRANE AND PART OF THE WALL OF THE LARYNX IN PSEUDOMEMBRANOUS LARYNGITIS.—(*Schmaus*.)

a. Cartilage. *b*. Submucosa, rich in glandular elements, also swollen and with some lymphoid-cell exudate. *c*. Line of the membrana propria. *d*. Pseudomembrane made up of fibrinous elements, in which are entangled leukocytes and desquamated fragmented epithelial cells. *e*, *e*. Gland-duct.

The membrane may be fibrillar,—that is, the fibrin coagulated in fibrillæ, or branching lines,—or the result of the coagulation may be a hyaline, homogeneous film, almost, if not quite, imperceptible. If the exudate be fibrillar, the membrane is clearly discernible during life; if hyaline, it may be quite invisible, even in the throat. Intermediate between the fibrillar and hyaline forms of the membrane is a finely granular deposit, resembling to a certain extent fragmented cells rather than a distinct fibrinous product. The hyaline and granular forms of the membrane—particularly the hyaline—resemble in stain reactions similar mucin-containing structures. The membrane may be laminated, especially in chronic cases; two, three, or even

[1] The essential facts concerning this process may be gleaned from Baumgarten's paper, in the "Berl. klin. Woch.," 1897.

four distinct layers may be shown on section. Sometimes these layers do not adhere to one another and may be separated or separable; the lamination is probably due to a layer of membrane forming, followed by a pause, during which a small quantity of mucus accumulates below, and then a second layer of membrane forms and another layer of semi-liquid exudate, and so on, until the cavity is freed of, or is filled by, the rapidly forming mass.

Occasionally, a rather extraordinary periodicity is observed in the appearance of the membrane: this is especially true of the chronic form,

FIG. 276.—FIBRINOUS CAST FROM THE BRONCHI, CASE OF CROUPOUS PNEUMONIA.[1]—(*Schmaus.*)

in which, exclusive of the pseudomembranous processes that may accompany menstruation, the membrane appears once each week, once each month, or at other stated intervals. Its appearance may be attended by fever or other symptoms; in the acute pseudomembranous inflammations this always occurs, but in the chronic types no symptoms, except the expulsion of the membrane, may precede, accompany, or follow its formation. Exfoliation or casting-off of the membrane may occur as

[1] Pneumonia is not a frequent cause of fibrinous bronchitis.

rapidly as it forms, or it may remain and be pushed off by developing mucus or continued functional activity. When removed, the surface of the basement membrane is exposed; but that tissue is not destroyed, and the pseudomembrane may be immediately reproduced, or, if the process be in a condition to terminate—the cause withdrawn—a catarrhal inflammation of the mucous surface ensues, and recovery follows exactly as in simple acute catarrhal inflammations. In chronic cases the tendency to recurrence of the process is manifested by repeated attacks, as in membranous endometritis, relapsing fibrinous bronchitis, and membranous proctitis. Of the chronic form occurring in the bronchi Osler says, "We know of nothing which can prevent recurrent attacks."

Sites.—There is no anatomic reason why pseudomembrane should not occur wherever catarrhal inflammation may develop. The acute pseudomembranous process is most frequent in the larynx, throat and nose, intestine, rectum, and middle ear, in the order named; the chronic form is most common in the uterus, rectum, bronchi, nose, and intestine, in the order given.

Hemorrhagic inflammation of mucous membranes is relatively rare. It accompanies intense infective processes and may be regarded as a manifestation of infection by intensely virulent bacteria or as the result of lowered resistance on the part of the patient. The condition probably does not merit a separate consideration, as it is nothing more than one of the previously described processes, or of gangrenous inflammation, accompanied by the presence of hemorrhage. Inflammations of this character may accompany diphtheria and diphtheroid anginas and the throat lesions of scarlet fever. It is also one of the conspicuous manifestations of dysentery. Inflammation of this type is observed in mucous membrane lesions that sometimes accompany acute septic processes such as puerperal fever and other forms of septicemia and also pyemia. In some cases of peritonitis, especially the fulminating septic form, an associated hemorrhagic inflammation of the colon, and, less frequently, of the small intestine and bladder, is sometimes observed. Inflammation attended by capillary hemorrhage may follow the application of escharotics and sometimes accompanies certain types of poisoning; hemorrhagic gastritis due to arsenic, carbolic acid, and other irritant poisons belongs with this group. The condition is to be differentiated from hemorrhage due to erosion, necrosis, or other lesion involving an artery or vein. In the latter group of cases, which includes bronchopulmonary hemorrhage, bleeding from gastric and typhoid ulcers, and allied conditions, the hemorrhage is from a vessel of some size; in the hemorrhagic inflammations the quantity of blood is rarely large and is derived from capillaries, the walls of which have been injured by the toxic agent to which the associated inflammatory process is due.

Morbid Anatomy.—As already stated, hemorrhagic inflammation is usually a complication; the affected tissues manifest the histologic changes of catarrhal, pseudomembranous, or gangrenous inflammations, and, in addition, are infiltrated by erythrocytes which have been extravasated from the injured capillaries. The affected membrane is blood-stained, the color varying from a pinkish-red to a dark crimson and in some cases purple or purplish-black. The surface is often strewn

with small shreddy coagula, and similar bodies are also present in the discharges. The hemorrhage is rarely abundant, although I recall an instance of hemorrhagic enterocolitis, due to combined puerperal sepsis and poisoning by intrauterine mercurial douches, in which the stools indicated large hemorrhages and led to the suspicion of typhoid ulceration. At the autopsy the intestine was distended by almost pure blood, although at no point could any alteration resembling an ulcer be detected. Histologically the changes of pseudomembranous, or more commonly gangrenous, inflammation are present. Erythrocytes in all stages of necrosis

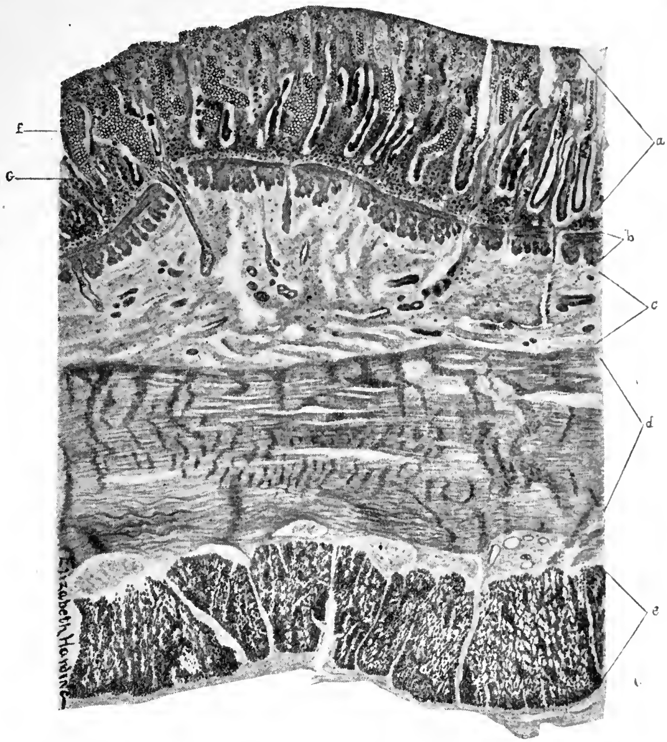


FIG. 277.—HEMORRHAGIC COLITIS. (Colon of a dog; colchicum poisoning of twelve hours' duration.)—(*Harris.* *a*. Mucosa. *b*. Muscularis mucosæ. *c*. Submucosa. *d*. and *e*. Muscle layers of the intestine. *f*. Blood between the gland crypts. *g*. Altered epithelium of crypt. The upper leader from *a* terminates in a layer of necrotic mucosa. The blood also occupies some of the crypts, the epithelium of all of which is necrotic. The submucosa is swollen.

are irregularly scattered through the affected tissue. At points the microscopic hemorrhages are around or adjacent to capillaries, in some of which ruptures may be discerned. Usually the process is diffuse, although occasionally it is singularly punctate. In other cases the diffuse and punctate forms occur together, giving rise to a reddened mucosa in which numerous hemorrhages may be observed. In exceptional instances large ecchymotic spots and submucous infiltration by blood are coincident. When associated with catarrhal or pseudomembranous inflammations, extending necrosis gives rise to changes indistinguishable

from those seen in the type of inflammation commonly called gangrenous. It is possible, although not probable, that when small areas are affected the blood may be removed without destruction of the involved mucosa.

Hemorrhagic inflammation affects particularly the colon (dysentery), pharynx, mouth, and nasal cavities; occasionally inflammations of the endometrium, bladder, urethra, and rectum are of this type. In toxic gastritis, and in the stomach lesions accompanying some infectious

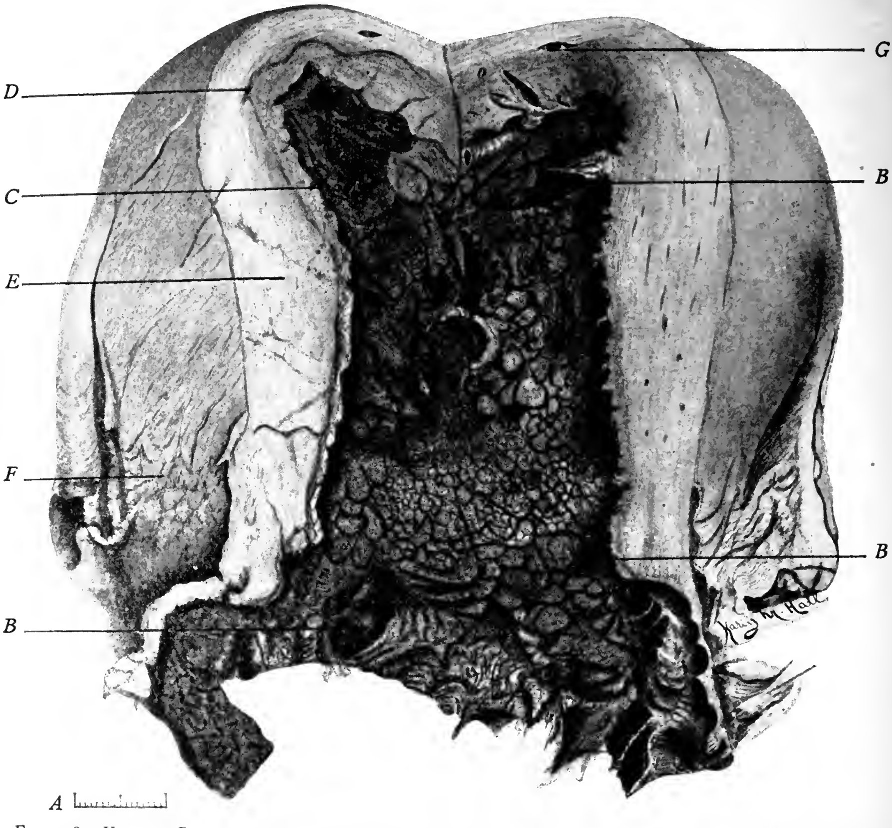


FIG. 278.—UTERUS CASE OF SEPTIC ENDOMETRITIS WITH EXTENSIVE NECROSIS OF THE ENDOMETRIUM AND MYOMETRIUM, DUE TO POSTPARTUM INFECTION. THE ORGAN HAS BEEN LAID OPEN BY INCISION THROUGH THE ANTERIOR WALL.

A. Scale, 1 inch. *B*, *B*, *B*. Cavities formed by extensive necrosis *C*. Necrotic zone that, on its inner surface, projects as a shaggy fragmenting stratum and externally is bounded by *D*, the line of hyperemia and leukocytic accumulation. (See Fig. 279.) *E*. Muscle layer not presenting any conspicuous gross lesion. *F*. Peritoneal surface; early stage of serofibrinous inflammation (the block of tissue from which the microscopic drawing, Fig. 279, was prepared was taken from just above this point). *G*. Thrombosed sinus.

diseases (yellow fever), the changes in the gastric mucosa are essentially hemorrhagic. In the hemorrhagic septicemias of man and lower animals the lesions occurring in the mucosæ are of this type. The condition may readily be produced by toxic doses of colchicum (see Fig. 277).

Inflammations Attended by Distinct Necrosis of the Mucous Membrane.—In some cases of catarrhal inflammation, and when pseudo-

membrane is formed, particularly in the latter instance, more or less necrosis restricted to the epithelial layer is usually present. The conditions at present under consideration differ from the preceding in the fact that tissue death extends deeper, involving the basement membrane, and frequently the submucosa. No little confusion exists as to the name which should be applied to the group of processes in which this change is observed. As the condition is commonly a manifestation of diphtheria, it was at one time known as **diphtheritic inflammation.** This term was utilized to differentiate diphtheria from croup, the prevailing belief being that they were distinct diseases. It is now known that the Bacillus diphtheriæ may cause both, and other inflammations as well, and that the disease clinically and bacteriologically called diphtheria may be manifested by pseudomembrane formation, or by necrotic processes extending deeper, or by both. In order to prevent the confusion resulting from the term diphtheritic, **gangrenous inflammation** has been substituted. The latter term, however, is objectionable because gangrene implies the death of larger masses of tissue than necessarily occurs in this connection. The *gangrenous sore throat* and *gangrene of the fauces*, also called *gangrenous angina*,—these terms were especially used by the older writers,—are forms of necrosing inflammation almost invariably due to the Klebs-Löffler bacillus.

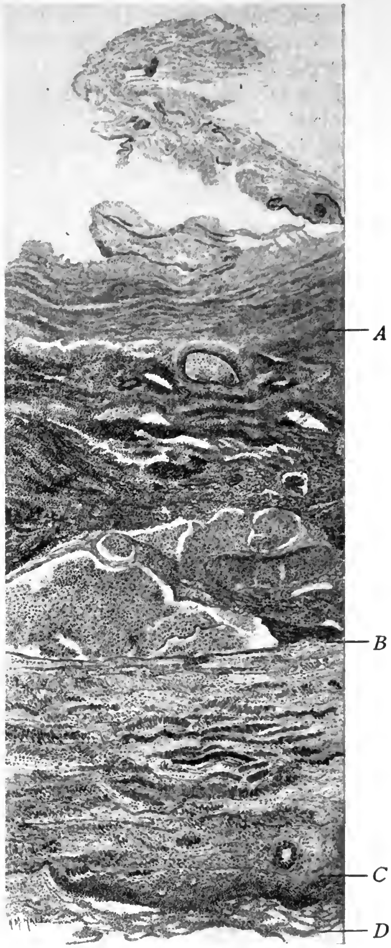


FIG. 279.—UTERUS, SECTION FROM SPECIMEN SHOWN IN FIG. 278. (Fixed in Zenker's fluid; paraffin-eosin, toluidin blue. Obj. Leitz 16 mm., oc. compensation, and reduced two-thirds.)

A. Above this point is the necrotic layer consisting of granular detritus containing enormous numbers of bacteria, fragmenting histologic elements, and leukocytes. *B*. From *A* to *B* is the zone of hyperemia, leukocytic invasion, and progressive mycotic infiltration. Numerous uterine sinuses as well as arteries are shown all occupied by thrombi. *C*. From *B* to *C* muscle showing coagulation necrosis. This part of the section is only a narrow rim of the actual muscle; nothing would have been gained by showing the entire thickness. Just above and to the left of *C* is an artery the endothelium of which is proliferating. *D*. From *C* to *D* is shown the greatly altered serous covering. The layer represented in the drawing is largely composed of fibrin with entangled leukocytes and endothelial cells.

Inflammation of the mucosæ attended by necrosis may follow burns, scalds, the application of escharotics, and trauma. Embolic occlusion of the nutrient vessels to an area of the mucous membrane may lead to death of the involved structures. In practically all the conditions manifested by gangrenous inflammation, throm-

bosis of the capillaries in the affected area occurs; in most instances the arrest in the capillary circulation is due to the same cause as, and is part of, the necrosis. I have, on two occasions, observed a most extensive proctitis follow the continuous use of opium and morphin in patients who used three to six grams of the latter each day by rectal suppository. Administration of mercury, antimony, or arsenic has been followed by gangrenous processes involving the mucous surfaces.

It is probable that *cancrum oris*, *noma*, or *gangrenous stomatitis* is due to a bacteritic factor, although Lingard's bacillus is not generally believed to be the cause. (See Diseases of the Alimentary Canal; also Gangrene, p. 256.) This disease occurs in debilitated children, and usually follows one of the acute infectious diseases, most commonly (fifty per cent. of the cases) measles.

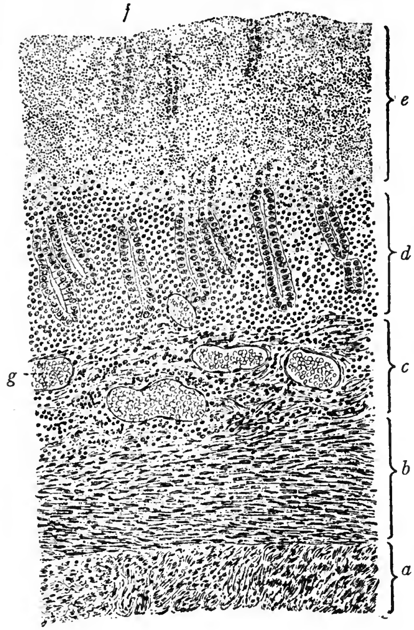


FIG. 280.—VERTICAL SECTION OF MUCOUS MEMBRANE, SHOWING DIPHTHERIC OR GANGRENOUS INFLAMMATION, FROM A CASE OF DYSENTERY.—(*Schmaus.*) × 40 diameters (?).

a b. Muscular layers. *c*. Submucosa with widely distended blood-vessels, swelling, and leukocytic infiltration. *d*. Adherent portion of the mucosa in which degenerative and necrotic changes are in progress and which fades off into *e*, the necrotic layer of the mucosa. *f*. Part of a gland in the necrotic tissue, the structure of the gland elements not having been, as yet, destroyed, although separating with the necrosed layer. *g*. Distended blood-vessel.

The necrotic processes affecting the mucosæ and due to infection by pyogenic cocci, or, less frequently, the pneumococcus, occasionally manifest a clearly gangrenous tendency. In tissues weakened by any associated lesion, and often when reduced resistance is not demonstrable, other bacteria, as the colon bacillus, typhoid bacillus, and the Bacillus pneumoniæ, may give rise to gangrenous processes.

Morbid Anatomy.—Whether the initial cause be infection or not, the circulation is arrested in the area involved, and coagulation necrosis promptly results; infection (primary, secondary, or multiple), is now assured, and disintegration follows. In other cases, the slough, after a varying period, may be detached and cast off, or remaining in position it is decomposed by bacteria; in other words, putrefies. As the necrotic area extends into the submucosa to a varying depth, the lymphatic system is widely opened and absorption of microbic poisons follows, with all the phenomena of grave septic intoxication. The plugs that occlude the vessels become infected and disintegrate, and hemorrhage may result; or bacteria (most commonly pyogenic cocci) gain ingress to the lymphatic system, and enlargement, and even abscess formation, in the nearest lymph-nodes may follow; or, bacteria reaching the blood give rise to septicemia. The necrosis may assume phage-

denic characters, followed by wide-spread destruction; this is probably due to a secondary infection, although, of course, it may have been primary, and is typified in noma, gangrenous inflammation of the labia in the female, and of the glans penis in the male. The initial process in the latter cases may have been a chancre or a chancroid. When involving the interior of the uterus, following labor or abortion (**septic endometritis**), the mucosa becomes necrotic and the process rapidly invades the myometrium, in the sinuses of which septic thrombi form. The resulting septic sinusitis may extend to the uterine and parauterine veins or even beyond, producing an extending thrombosis, which, by impeding the circulation and disseminating bacteria, furthers the progress of the necrosis.

This form of inflammation is most common in the tonsils, pharynx, mouth, external genital organs, rectum, and colon, but is not infrequent on other membranes as well. The author has observed a severe gangrenous cystitis that followed prostatic abscess with urinary infiltration.

Suppurative and pustular inflammations of the mucous membranes are sometimes observed in pyemia, septicemia, smallpox, and, rarely, in other infectious febrile processes. Erysipelas of the mucous membrane may be followed by suppuration. Diphtheria may, by rendering mixed infection possible, give rise to pus formation in the submucosa. Pyogenic infection of the submucosa results from abrasion or destruction of the protective epithelium, or from the accumulation of infective material in a mucous gland with obstructed duct; the basement membrane of the gland, being less resistant than the overlying tissues, distends and ruptures into the submucosa, leading to infection and pus-formation in the affected tissues. This is probably the process giving rise to suppurative tonsillitis and allied conditions.

In some cases of mucous membrane inflammation the exudate is composed largely of polymorphonuclear leukocytes and the condition is due to organisms of fully established pyogenic properties. This type of mucous membrane inflammation is commonly produced by the gonococcus, in which case the process is called **gonorrhea.**[1] When due to other pyogenic organisms it is known as **suppurative catarrh.** Catarrhal inflammations characterized by purulent or mucopurulent discharges attack particularly the urethra and birth canal, but may also involve the mucosa of the nose and bronchi, the conjunctiva, and middle ear. An essentially similar condition affects the Fallopian tube (**suppurative salpingitis**) and, as a result of occlusion of the two ends of the tube, the pus accumulates in the resulting cavity (**pyosalpinx**). In some of these conditions the pyogenic organisms enter the submucosa in sufficient numbers to induce suppuration. In this way **periurethral abscess** complicating gonorrhea, and the cellulitis involving the pharynx and the areolar tissues of the floor of the mouth (**Ludwig's angina**), are produced. In some cases the infiltration is rather diffuse, the polymorphonuclear leukocytes being distributed in the lymph-spaces and not aggregated to form abscesses. Suppurative interstitial gastritis may be mentioned as a type of this form of submucous infection. In many cases the bacteria penetrate the submucosa from the surface, but it is also possible for the same result to follow hematogenous infection.

[1] See p. 107.

Suppurative processes are usually situated in localities liable to injury and accompanying infection, or in membranes rich in sulci affording lodgment for substances containing bacteria that subsequently give rise to infection; aside from the specific diseases, such as small-pox, in which the suppuration occurs in the form of pustules in the mouth and adjacent membranes, the most common sites of the process have been indicated. In the appendix the infection and pus-formation in the submucosa may find less resistance to egress toward the peritoneum than toward the mucous tract, and hence **appendicitis** not uncommonly gives rise to infection of the serosa. In similar obstructive conditions affecting the Fallopian tubes, rupture into the peritoneum may afford a more favorable route for the infection and emptying of the distended tube than escape into the uterine cavity. While the foregoing reference to appendicular and Fallopian disease is made under Suppurative Inflammation, it is not to be forgotten that accumulated catarrhal material contains abundant infectious agents, and that its escape will as certainly be followed by septic inflammation as though an abscess had poured its contents into the serous cavity. Suppurative and gangrenous processes are not uncommon in the appendix, and it does not seem probable that the Fallopian tube, once infected, would be less liable to the same processes.

FIG. 281.—INTESTINE, CHRONIC SECONDARY TUBERCULOSIS; IRREGULAR ULCERS THE FLOORS OF WHICH PRESENT A NECROTIC SURFACE. THE ULCERS ARE TRANSVERSE TO THE AXIS OF THE BOWEL.

Chronic infectious inflammations of the mucous membranes are of the greatest importance, and deserve the closest study. For the most part they, from the beginning, involve the essential function of the mucous surface by invading the submucosa. Included under this head are tuberculosis, leprosy, syphilis, glanders, actinomycosis, and rhinoscleroma.

Tuberculosis of the mucous membranes, independent of pulmonary tuberculosis, is not a rare condition. In the upper air-passages it is a most frequent occurrence in tuberculous patients, arising in the larynx, in the bronchi, and occasionally in the nose. Tuberculosis of the alimentary canal has been noted in every structure from the lips to the anus. The cause is the bacillus of tuberculosis, which has been considered in the section on Bacteriology. (See Tuberculosis, p. 144.)

Morbid Anatomy.—The infection may be from the surface or by the blood or lymph. Commonly the entrance of tubercle bacilli into the submucosa is promptly followed by the development of miliary tubercles, usually around or near a blood-vessel. In marked cases of general miliary tuberculosis the tubercles can be seen at many points in the mucous membrane. A little later these bodies coalesce and

by obliterative changes induced in the blood-vessels, deprive the basement membrane and overlying epithelium of their proper nutrition; by this time, through confluence, necrosis, and softening, a cheesy area develops, and, breaking through the basement membrane the caseous material is discharged and an ulcer results. The long axis of the ulcer is usually transverse to the long axis of the membranous tube—a condition due to the usual circumferential distribution of the blood- and lymph-vessels. External to the area of ulceration new fibrous tissue develops and contracts, in many localities giving rise to stenoses. When examined in its earlier stages, the condition is known as miliary tuberculosis; and later, when ulceration has ensued, or in the stage of caseation, as ulcerative or caseous tuberculosis, respectively.

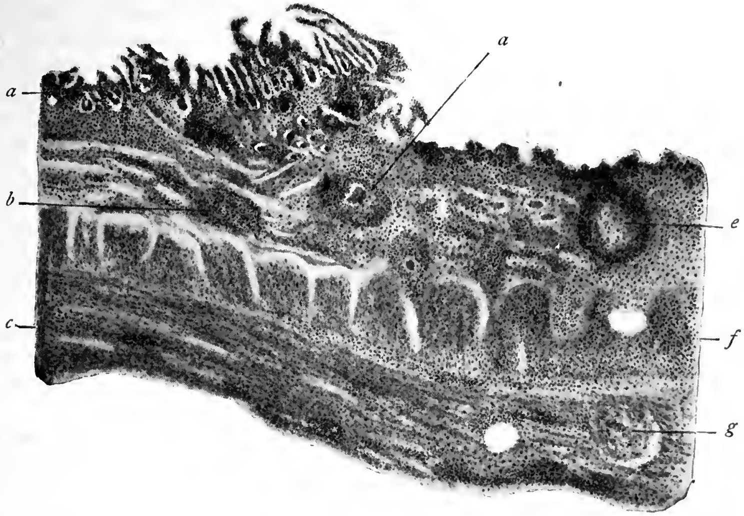


FIG. 282.—MARGIN OF TUBERCULOUS ULCER OF THE INTESTINE.
Specimen hardened in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin, and mounted in balsam. *a*. Mucosa that, as it approaches the ulcer, is swollen and thickened, with fragmented and desquamating cells. *b*, *d*, and *e*. Tubercles situated in the submucosa; *b* and *d*, and a tubercle just under and to the right of *d*, each show a central giant cell. The tubercle *e* shows central softening and beginning caseation. Note the extensive infiltration of the submucosa with small lymphoid cells, which, immediately under the ulcer, at *f*, have invaded the circular muscle-fibers. *c*. The longitudinal muscular layer, which, at *g* contains a solitary tubercle. (¼-inch objective; 1-inch ocular.)

Rarely, calcareous changes may occur and, as a result of infiltration with lime salts, the tubercle becomes quiescent, and the process is arrested. Occasionally in the mucous membrane of the intestine, particularly in the ileocecal area, and rarely in other mucosæ, the affection is characterized by the production of a large amount of fibrous tissue and great thickening of the submucosa, constituting what is called **chronic hyperplastic tuberculosis.**[1] The anatomy of tubercles, their method of infection, etc., have been considered with tuberculosis[2] in general.

[1] See p. 153.
[2] See Morbid Anatomy of Tuberculosis, p. 149; also tuberculosis of the various mucosæ, alimentary canal, organs of respiration, urinary organs, etc.

Leprosy[1] **of the Mucous Membranes.**—In purely anesthetic leprosy the only involvement noted by observers is in the colon, where ulcers are said to develop without leprous tubercles. Tubercular leprosy is prone to attack the mucous membranes, especially the conjunctiva, cornea, larynx, and nose. The leprous tubercles, like those of tuberculosis, occur around the blood-vessels in the submucosa; as the process extends, the blood-supply is cut off by the obliterative changes in the vessels, and a fibroid area results. Ulceration is not inevitable, or even frequent, as in tuberculosis. Sometimes, however, the leprous infiltration is followed by pyogenic infection, softening, and ulceration. The disease is due to the Bacillus lepræ, which has been considered when dealing with bacteria.

Syphilis[2] **of the Mucous Membranes.**—In primary syphilis the lesion is far more frequent in the mucous membrane than in the skin. The submucosa becomes infiltrated with small round cells, in which epithelioid and giant cells may be found; the blood-supply to the surface is cut off by obliterative changes in the arteries, and ulceration, or rather coagulation necrosis, ensues. The roseolar rashes of the secondary stage leave no discernible lesion. The mucous patches and ulcers are the result of coagulation or liquefaction necrosis, and occur in the mucosa of the tongue, pharynx, tonsils, palate, gums, and cheeks, and also on the mucous membrane of the anus and genital organs.

The lesion of tertiary syphilis affecting the mucous membranes is the gumma, which occurs in the submucosa, develops like the previously considered infective granulomata, and, when untreated, usually undergoes necrosis and ulcerates. As the ulcer heals, contracting cicatrices give rise to strictures; these are most frequent in the larynx, rectum, and esophagus. (See illustrations of syphilitic stenosis of the larynx and trachea, Fig. 286, p. 573.) Should cicatrization occur, without ulceration, contraction is equally sure to follow, but is less obstinate.

Glanders[3] **of the Mucous Membranes.**—This disease, due to the Bacillus mallei, manifests itself usually in the nose as ulcers brought about by the development of glanders nodules, made up of lymphoid and epithelioid cells in the submucosa, which, by necrosis, give rise to an ulcer. In the acute form gangrenous and septic phenomena not uncommonly accompany the process; in the chronic form the ulcers may be mistaken for those due to protracted catarrhal, tuberculous, or syphilitic disease. Demonstration of the bacillus is essential to an accurate diagnosis.

Actinomycosis[4] **of the mucous membranes** is most common in the tissues about the mouth and in the alimentary canal, especially the ileocecal area, but may affect other mucosæ. The ray fungus, like other chronic infections, gives rise to a collection of granulation tissue in the submucosa. The infiltration may be indurative with but little tendency toward necrosis; in other cases softening and suppuration are followed by necrosis of the overlying mucous membrane, producing an ulcer. The diagnosis is made by the demonstration of the fungus in the discharges

[1] See Bacillus lepræ, p. 157; also forms and manifestations of leprosy, pp. 158 and 159.

[2] See Syphilis, p. 174; Histology of Chancre, p. 177; Mucous Patch and Gumma, pp. 179 and 180.

[3] See Glanders, pp. 160 to 162.

[4] See Actinomycosis, p. 166; also Paths of Infection in Morbid Anatomy of Actinomycosis, p. 168.

or in sections of the infected tissue. The new formation is usually surrounded by a zone of proliferating connective tissue, which, in the jaw, has been mistaken for sarcoma. Sooner or later suppuration ensues.

Rhinoscleroma[1] consists in the thickening and tumefaction of the submucosa of the nose, rarely extending to the pharynx or larynx; the affection usually begins in the nose. The indurated areas are at first red or pink, and are very tender; later they become white. The disease is alleged to be due to a bacillus found in the tumefied tissues, usually in the hyaline cells of the fibrous meshwork. Rhinoscleroma is rare in this country, and clinically resembles lupus. It is essentially chronic as to time, requiring years to develop fully.

Thrush[2] is a disease largely restricted to the mucous membranes, usually affecting the mouth, in which location the condition is called **mycotic stomatitis.** The mucosa of the esophagus is sometimes involved, and other parts of the alimentary canal less frequently.

The **tumors** which may occur on or in mucous membranes are numerous, and, as certain localities seem liable to special varieties, it is thought best to record the neoplasms and cysts with the special pathology of each region.

[1] See Rhinoscleroma, p. 159.
[2] See p. 165.

CHAPTER VIII.

ORGANS OF RESPIRATION.

Anatomic Divisions.—The anatomist divides the organs of respiration into the *nose* or *nasal cavities*, *larynx*, *trachea*, *bronchi*, and *lungs*. For physiologic consideration it is important to recognize a conducting part, including all but the lungs, in which the essential chemistry and vital phenomena of respiration occur. Incidentally, other functions are performed by the various parts of the whole, one function being accessory to another,—*e. g.*, olfaction in the nose, vocalization, etc., in the larynx,—all aided by and dependent upon the various muscular and bony structures of the chest with its complex innervation.

NOSE.

Malformations.—The nose may be absent, *arrihinia*, or may be represented by a teat or a snout-like projection as in *cyclopia* or *synophthalmia* —a malformation consisting of a single orbital cavity, centrally located, and containing one or two eyeballs in varying stages of development; rarely, the eye is absent. Other malformations of the nose consist in absence of one or more muscles, clefts of the alæ, deviations and faulty development of the septum, incomplete development of some of the bones entering into the formation of the cavity, constriction of the nares, more or less complete, and clefts in the floor of the nasal cavity, usually associated with faulty development of the lip, palate, or other soft parts. According to Boulay,[1] there are 80 recorded cases of congenital occlusion of the nares. The occlusion was unilateral in 39 of 65 fully reported instances; in 51 it was osseous, partly osseous in 7, and membranous in 7. The deviation of the nasal septum (**scoliosis septi**[2]) may be unilateral, bilateral, zigzag or irregular; the inclination may be (1) toward one side (simple deviation), (2) vertical sigmoid, one or more convexities directed toward each fossa, or (3) antero-posterior sigmoid.

Hemorrhage from the nose (**epistaxis**) occurs as the result of injury, either directly applied to the nasal structures, or falls and blows severely jarring the head, and in fractures involving the base of the skull. Extreme plethora is asserted to be a cause; bleeding from the nose may be produced by hyperemia, either premonitory to inflammation or secondary to overexertion and forcible cardiac action; violent respiratory acts, like strangling, coughing, or sneezing; intracranial congestion and hyperemia; the passive congestions of heart disease and obstructed return of blood from the head, as in tumors pressing on the veins of the neck; occasionally the hemorrhage is vicarious, as in arrested menstruation and suspended excretion (*e. g.*, sweating and suppression of urine); severe

[1] "Arch. de Méd. des Enfants," March, 1902.
[2] Sheedy, "The Postgraduate," Oct., 1902, p. 1130.

vomiting; tumors, ulcerations, etc., of the nasal mucosa; blood diseases, like hemophilia, scurvy, leukemia, etc. Epistaxis is also seen in the early stages of some of the acute infectious diseases, most commonly typhoid fever. Renal disease, associated with a rise in blood-pressure, and cirrhosis of the liver are also causes. Martinet[1] lays particular stress upon the occurrence of epistaxis in arteriosclerosis and believes that the condition is due to the associated hypertension. Osler[2] has described a form of epistaxis due to multiple telangiectases of the nasal mucosa. In some cases the hemorrhage appears to come from the ethmoidal veins and possibly from other sinuses.[3] Death from epistaxis is rare. The quantity of blood lost varies, but usually stops short of danger. When bleeding is repeated, there is not infrequently some local lesion to account for it, such as erosion or ulceration, usually situated on the septum. Varicosity of the veins of the nasal mucosa may sometimes be recognized.

Inflammation[4] of the nasal mucosa is called **rhinitis.** Any of the already described mucous membrane inflammations may occur in the nose. **Acute catarrhal rhinitis,** acute nasal catarrh, or coryza is the most frequent of the inflammations affecting the nasal mucosa. Of the many conditions believed to be operative in the production of acute catarrhal rhinitis, infection is most important. Cold and exposure, irritants, such as ammonia, and superheated gases are said to be etiologic factors. Cold and exposure are probably of secondary importance, and act by increasing the susceptibility of the membrane to infection. There is, at times, evidence indicating that the condition is contagious The inflammatory process secondary to infectious diseases, such as influenza and typhoid fever, should be mentioned.

Fibrinous and gangrenous inflammations of the nose may be primary, but are more frequently associated with or secondary to a primary pharyngeal lesion. **Pseudomembranous rhinitis** is, in a certain percentage of cases, a nasal manifestation of diphtheria.[5] This statement applies not only to the acute forms, but to the more chronic cases as well. Some of the latter show a persistent, rather long-continued pseudomembranous inflammation; the diphtheria bacillus is present in the exudate, and, in rare instances, has constituted the starting-point for an epidemic of diphtheria. Pneumococci, streptococci, staphylococci, Friedländer's bacillus, and other organisms occasionally produce a false membrane in the nose. Pseudomembranous rhinitis from other causes occurs, but is infrequent. **Chronic catarrhal rhinitis,** also called *chronic nasal catarrh*, usually follows repeated severe attacks of acute inflammation, although occasionally it comes on insidiously and may induce lesions of considerable magnitude before symptoms appear. Inhalation of irritants and dust and the presence of foreign bodies are also causes. Various constitutional vices—such as chronic heart disease, tuberculosis, syphilis, anemia, etc.—are also important causes. The extreme aridity of houses heated by modern methods undoubtedly pre-

[1] "La Presse Méd.," April 6, 1904.
[2] "Bull. Johns Hopkins Hospital," Nov., 1901, p. 333. Reference to previous reports.
[3] Kelly, "Lancet," Feb. 24, 1900.
[4] For pathology of inflammations of the mucous membranes see p. 546.
[5] For references to literature on nasal diphtheria consult article by Wilner, "N. Y. Med Jour.," Nov. 5, 1904, p. 881.

disposes to catarrh. The presence of tumors, particularly of polypi, is said to favor the condition, or may be an important determining cause; in other cases overgrowth of the mucous membrane may assume a polypoid character, a fact supporting the view that the inflammation leads to tumor formation. The inflammatory processes may be *hypertrophic* or *atrophic*, and may or may not be associated with fetid discharge (**ozena**). There is a form of nasal inflammation that has received the name **purulent rhinitis,** by reason of the pus-like character of the discharge; an inflammation of this kind not infrequently follows the presence of foreign bodies, nasal tumors, suppurative processes in accessory sinuses, acute infection, such as gonorrhea, and the ulcerative stages of the chronic infections, particularly glanders, tuberculosis, and syphilis. Under the name of **caseous** or **scrofulous rhinitis**[1] has been described a chronic process indicated by the production of caseous material which often accumulates in the affected nasal fossa; the condition is probably not a manifestation of tuberculosis except in rare cases; a leptothrix has been found in the material, and it is possible that the affection is a form of pseudo-tuberculosis.[2]

Tuberculosis of the nasal mucosa may be primary or secondary. Renshaw[3] collected 116 cases of **tuberculous rhinitis,** 30 of which were primary. In the former group ulceration was conspicuous, and in the latter, the polypoid form was most frequent. **Syphilis** is frequently the cause of nasal catarrh and may give rise to ulcerative processes; gummata of the tissues forming the facial nose are not infrequent. **Glanders** is often primary in the nose. **Leprosy** and **actinomycosis** sometimes attack the nasal mucosa or contiguous tissues. **Rhinoscleroma** nearly always begins in the nose.

The nasal mucosa being continuous with that of the sinuses of the superior maxilla, the frontal and ethmoid bones, and by the Eustachian tube with the middle ear, inflammation once established in the nose may extend to these structures, where, by reason of faulty drainage, and inaccessibility, chronic processes ensue. The sinuses lying in proximity to the brain may afford means for intracranial infection, as seen in middle-ear disease leading to cerebral abscess, and in the tuberculous meningitis asserted to follow tuberculosis of the nasal cavities and their appendages.[4]

Tumors.—*Adult Epithelial.*—*Adenomata* of the nasal mucous membrane occur more commonly as the pharynx is approached, but, on the whole, are not frequent; they are mostly cystic, owing to inclusion of a mucous gland, ordinarily by inflammatory tissue. *Papillomata* or warts are usually situated in the vestibule; in children they are frequently of syphilitic origin. A hairy papilloma resting on a base of fat (lipomatous tissue) has been described. It is believed to be congenital (Arnold). *Carcinoma* of the nose is rarely primary, usually extending to the nasal cavity from the mouth or face; it is generally of the epitheliomatous type rather than glandular. Schmidt found five carcinomata of the nose and throat in 32,997 patients. *Fibromata,*

[1] Bark, "Jour. of Laryngology, Rhinology and Otology," Dec., 1903.
[2] See foot-note p. 156.
[3] "Jour. of Path. and Bact.," Feb., 1901.
[4] For literature on diseases of the accessory sinuses of the nose, see Howard and Ingersoll, "Amer. Jour. of Med. Sci.," May, 1898; also Kirkland, "Australasian Med. Gazette," 1902, vol. xxi, p. 299.

chondromata, *osteomata*, and *myxomata* occur. True myxoma is rare, but *fibromyxoma* and pure fibroma are of not infrequent occurrence; some *nasal polypi* belong to one of the two varieties. Wright[1] maintains that nasal polypi are not myxomatous but result from serous infiltration of the submucosa and hyperplasia of the superficial layers. *Sarcomata* occur in the nasal cavity, arising from the fibrous tissue of the submucosa, the periosteum, or, rarely, the bone; they occasionally develop in the sinuses: *e. g.*, the antrum of Highmore.

Erectile tumors (**telangiectatic polypi**) are made up of numerous thin-walled blood-vessels embedded in a fibrous, mucoid, or adenomatous matrix containing more or less myxomatous tissue. They are infrequent.

Postnasal Adenoids.[2]—There must be some doubt as to the advisability of regarding these enlargements as true tumors, and, as the new growth is most frequently the result of an increase in pre-existing lymphoid tissue, the term **postnasal adenoid hypertrophy** has been applied. The disease is one of infancy and childhood, most frequent in tuberculous families, and is commonly associated with some form of rhinitis, with defects of development in the osseous walls causing stenosis, and with concomitant pharyngeal or postnasal catarrh. The growth is most marked on the posterior rhinopharyngeal wall. The masses are usually sessile, with uneven, granular, or lobulated surfaces.

Histologically, the growths are composed of hyperplastic lymphoid tissue in which the quantity and density of the reticulum vary. The fibrous tissue is mostly perivascular. The epithelium covering the mass may be squamous or columnar; the latter is sometimes, although rarely, ciliated; a basement membrane can usually be detected. The epithelium and sometimes the deeper tissue is necrotic. The crypts are often deeper than normal and are not infrequently filled with caseous material. So far as the growth itself is concerned, it usually atrophies and disappears at or about puberty. In the mean time, however, the mechanical interference with respiration, and the associated catarrh, induce a drain on the patient's general health, embarrass respiration, and may be accompanied by tuberculous infection. Dieulafoy found tubercle bacilli in twenty per cent. of the adenoids examined; of the seventy-five studied by Lartigau and Nicol, eight contained tubercles and bacilli, and four bacilli without tubercles. Involvement of the Eustachian tube and an infective otitis media, with consequent deafness, are not infrequent complications.

Rhinoliths are calcareous masses occasionally found in the nose; they arise from the deposit of lime salts around a nucleus, usually a foreign body, or, rarely, from inspissated secretion. Of 125 cases collected by Hall,[3] the largest concretion weighed a little over 45 grams.

Anosmia, or loss of the sense of smell, may be caused by (1) central lesions or (2) chronic catarrhal thickening, and contraction may

[1] "N. Y. Med. Record," Jan. 26, 1901. See also Yonge, "Brit. Med. Jour.," Nov. 5, 1904, p. 1239.

[2] Lartigau and Nicol, "Amer. Jour. of Med. Sci.," June, 1902; Marsh, "Lancet," June 7, 1902. Courtade, "Archives internationales de laryngologie, d'otologie et de rhinologie," Mars-Avril, 1903. Simpson, "Adenoid Growths of the Naso-Pharynx," 1904. Harris, "Amer. Med.," Jan. 2, 1904, p. 20. Holz, "Berl. klin. Woch.," Jan. 23, 1905.

[3] "Trans. of Clin. Soc. of London," vol. 26, p. 60.

pinch the filaments of the nerve, and thereby destroy them; a similar result may follow periosteal thickening, as seen in syphilis. When the sense is not destroyed, but perverted, the term **parosmia** is used. *Hyperesthesia of the olfactory nerves*, also called **hyperosmia,** is usually dependent upon central lesions or is a part of some neurosis. Exclusive of the abundant exudate seen in inflammations, and independent of any recognizable change in the membrane of the nasal cavity and accessory sinuses, there is, at times, a most marked serous discharge, constituting a true **rhinorrhea.** The cause of the condition is not known. The case reported by Glynn[1] manifested symptoms simulating an intracranial tumor, but entirely recovered after a profuse discharge from the nose of a liquid believed to have been cerebrospinal fluid. The reporter was of the opinion that an internal hydrocephalus had drained through the perineural sheaths of the olfactory nerves. Thompson maintains that spontaneous rhinorrhea of cerebrospinal fluid is always the result of internal hydrocephalus.

LARYNX AND TRACHEA.

Normal Structure.—The epithelial layers of the mucosa vary as to depth and variety of epithelium; the epiglottis and the true cords are covered by squamous epithelium, lines of which extend between the epiglottis and cords. The greater area is covered by ciliated epithelium.

Malformations.—*Absence* of the larynx is rare. Occasionally, it is small and poorly developed (*hypoplastic*), a condition said to attend testicular hypoplasia and to follow castration. Abnormal largeness is at times noted. Combinations of the last-named conditions, giving rise to asymmetry, are more frequent. The ventricles may be abnormally large, or aberrant sinuses or pouches may extend into the perilaryngeal tissues, giving rise to a condition known as *emphysema of the neck*, or *aerocele*. From faulty union of the branchial arches fistulas may result. Clefts and fissures of the epiglottis occur. Defects in the laryngeal cartilages are sometimes observed, but are rare. Franckel[2] reports two instances of membranous diaphragm in the larynx; similar cases are recorded by Harmer[3] and Fein[4]; the latter collected 11 reported cases. Simmonds[5] describes various forms of flattening and distortion of the trachea occurring in the aged. He has collected sixty-one cases; fifty-eight of the patients were males. All were over fifty years of age. In some cases the trachea is irregularly dilated; the ectasia results from yielding of the elastica.

Hemorrhage[6] from the larynx accompanies injury, severe inflammations, tubercle, and tumors, particularly the highly vascular papillomata and carcinomata; it rarely occurs from vascular distention and vicarious function. Hemorrhages into the submucosa, and even on the free surface, are sometimes present in scurvy, leukemia, perni-

[1] "Med. Soc. of London," Feb. 13, 1905.
[2] "Deut. med. Woch.," Dec. 18, 1902.
[3] "Wien. klin. Woch.," Nov. 13, 1902.
[4] "Wien. klin. Rundsch.," Dec. 27, 1903.
[5] "Virchow's Arch.," 1905, Bd. 179, p. 15.
[6] See Rhodes, "Jour. Amer. Med. Assoc.," Oct. 29, 1904, p. 1284; bibliography.

cious anemia, and allied blood dyscrasias. Suffocation and strangulation are also causes. Intense hyperemia and extreme congestion may produce laryngeal hemorrhage. When the condition accompanies inflammation, it is called **hemorrhagic laryngitis;** Garrel recognizes three forms of laryngeal hemorrhage: (1) traumatic, due to injury; (2) the dyscrasic, resulting from blood conditions and systemic vices; and (3) organic, due to ulceration, tumors, and other pathologic processes affecting the larynx.

Hyperemia occurs in the initial stage of inflammation, after violent exercise, inhalation of irritants, etc.

Congestion is noted in heart disease and lesions obstructing the return of blood from the larynx, as goiter and mediastinal tumors.

Inflammations.[1]—Inflammation of the larynx is called **laryngitis;** of the trachea, **trachitis** or **tracheitis.** Catarrhal, pseudomembranous, and gangrenous inflammations occur in the order given; the last is infrequent, and the catarrhal is common.

The catarrhal inflammations may be either acute or chronic, the former depending upon exposure, inhalation of irritant gases, extension of inflammation from adjacent mucosæ, infections and infectious diseases, such as measles, influenza, etc. Follicular distention and superficial erosions occur, but are infrequent. The vascular distention of acute inflammation, with even slight edema, interferes with the function of the vocal cords, narrows the orifice, and is the anatomic basis for the so-called **spasmodic laryngitis,** which is also known as *spasmodic*, *false*, or *catarrhal croup*.

Chronic catarrhal laryngitis is usually a sequence of repeated attacks of acute inflammation. It is favored by continuous exposure to irritation, by the presence of constitutional vices,—such as syphilis, tuberculosis, contracting kidney, gout, etc.,—and by local disturbances of nutrition, such, for example, as are seen in the stagnant circulation of chronic heart disease and in long-continued pulmonary inflammation, emphysema, etc. Epithelial thickening (**pachydermia laryngis**) of the vocal cords, submucous cellular infiltration, and even papillomatous excrescences may result. Rosenberg regards singer's nodes as results of inflammation involving the duct of Fränkel's glands, and not true epithelial indurations (pachydermia), as believed by Virchow.

Pseudomembranous laryngitis, or **membranous croup,**[2] is almost exclusively dependent upon the bacillus of diphtheria, which here rarely induces gangrenous lesions similar to those occurring on the pharynx and tonsils. Menetrier[3] reports a case of membranous inflammation of the air-passages in which an actively virulent pneumococcus alone was found. Catarrhal and pseudomembranous inflammations of the larynx are sometimes attended by bleeding, but altogether hemorrhages are rare.

Suppurative laryngitis occurs as a pustular manifestation in smallpox, or as a purulent infiltration of the submucosa, most commonly secondary to an antecedent edema of that tissue. Pus-formation may be diffused in the submucosa or may be circumscribed (abscess); in the latter case it may rupture into the larynx, infiltrate the perilaryngeal tissues, or dissect into the esophagus. If evacuation be established and drainage secured, repair may follow.

[1] See Pathology of Inflammation of the Mucous Membranes, p. 546.

[2] See p. 550. [3] "Soc. Méd. des Hôp. de Paris," Dec. 9, 1904.

Catarrhal, pseudomembranous, and gangrenous inflammations sometimes complicate typhoid fever.[1] Necrosis of the cartilage probably secondary to a perichondritis is the most common; of Keen's collection of 221 cases, at least 89 affected the cartilages. The condition is fatal in about ninety-five per cent. of the patients in whom the cartilage undergoes necrosis. Ulcerative and suppurative lesions are less frequent. In some cases the laryngeal complication is due to the typhoid bacillus; in others it depends upon concurrent infection probably resulting from the lowered resistance of the patient. A typic **typhoid ulcer of the larynx** has been observed. In some cases the condition resembles Ludwig's angina; the epiglottis may be affected.

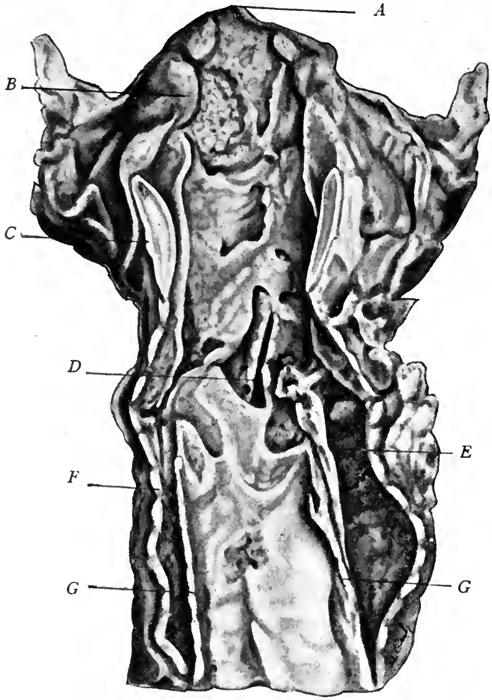


FIG. 283.—PSEUDOMEMBRANOUS LARYNGITIS AND TRACHEITIS DUE TO THE BACILLUS DIPHTHERIÆ. (From adult female; laryngeal diphtheria; death on sixth day. The membrane extended into the bronchi.)

A. Tip of epiglottis, just below which is an irregular necrotic area continuous with the pseudomembrane. *B*. Edematous and necrotic mucosa. *C*. Cartilage. *D*. Tracheotomy wound around which the pseudomembrane has become softened and detached; the tracheal cartilages are projected toward the observer as a result of spreading open the tube. *E*. The mucosa at and below leader from letter *E* is suffused with blood. *F*. One of the tracheal cartilages. *G*, *G*. Pseudomembrane for the most part detached from underlying mucosa.

Tuberculosis of the larynx[2] may be primary or secondary; the latter is the more common. The studies of Meyer and Ostowsky indicate that the bacillus may reach the submucosa without any discernible lesion in the overlying epithelium. It may begin by superficial erosive ulceration, but is usually manifested by a tuberculous infiltration of the submucosa, which may be diffuse or localized; in the latter case it resembles the chronic hyperplastic tuberculosis.[3] In typical cases of this form, sometimes called hypertrophic, ulceration occurs late, if at all. According to Theisen, the lesion is practically always secondary to pulmonary

[1] For fuller consideration of typhoid affections of the larynx, see Keen, "Surgical Complications and Sequels of Typhoid Fever," 1898. Also, Quinlan, "Laryngoscope," Jan., 1905, and Dupuy, "N. Y. Med. Jour.," Dec. 26, 1903, p. 1226.

[2] Meyer, "Virchow's Arch.," Bd. 165, H. 3, p. 498. Ostowsky, "Thèse de St. Petersburg," 1900. Thomson, "Phila. Med. Jour.," Sept. 14, 1901. Moller and Rappoport, "Zeit. f. Tuberk. und Heilstat.," July, 1903. Theisen, "Amer. Jour. of Med. Sci.," Nov., 1903, p. 833. Yankauer, "Laryngoscope," St. Louis, March, 1904. Frese, "Münch. med. Woch.," March 29, 1904, p. 552. Griffin, "Med. Record," Dec. 17, 1904, p. 975.

[3] See p. 153

involvement, and may be preceded by ulcerative lesions. Sometimes the hyperplasia is sufficiently circumscribed to justify the term **tuberculoma** of the larynx. According to Griffin, tuberculous ulcers usually are on the posterior wall, and begin low and ascend; syphilitic lesions arise above and descend. Cicatrization and contraction are common in syphilis and infrequent in tuberculosis. Although rare, syphilitic and tuberculous ulcers may be side by side and differentiation of the gross lesions is sometimes impossible. The histologic diagnosis can be made by the presence of anatomic tubercles, or granulation tissue, containing the bacillus. In cases of primary laryngeal tuberculosis secondary invasion of the lung can confidently be predicted.

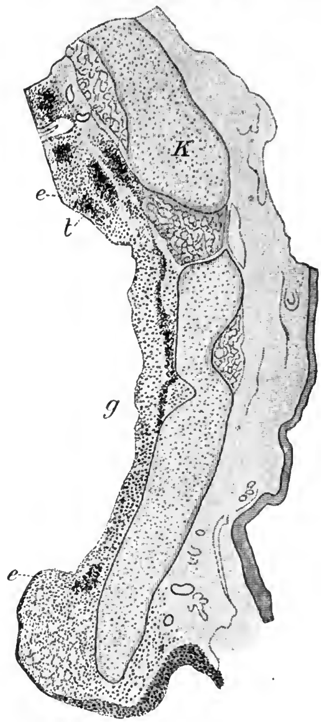


Fig. 284.—Tuberculous Ulcer of the Mucous Membrane of the Trachea. Vertical Section of the Tracheal Wall.—(*Schmaus.*) × 10 diameters.

K. Cartilage. *e, e.* Epithelial layer of the mucous membrane. *t.* Tubercles in the mucous membrane. (Submucosa.) *g.* Ulcer extending from *e* to *e.*

Syphilis of the larynx[1] may occur in any stage of lues. Apparently Moure's case is the only recorded instance of epiglottic chancre. Mucous patches are sometimes observed on the epiglottis, and less commonly on the ventricular bands; they are usually unilateral, oval or elongated, whitish or yellowish in color, 8 to 15 mm. in diameter, and marginated by a distinct red areola. Tertiary syphilis of the larynx may be ulcerative, gummatous, or cicatricial. The last form is the result of reparative efforts in either of the first two. Syphilitic ulceration may be rapid, but is usually slow; commonly cicatrization is present in one area and progression in another. Associated edema may be marked, and hemorrhage is occasionally present but rarely severe. The ulceration may extend to the perichondrium, and give rise to perichondritis and even necrosis of contiguous cartilage. In a case reported by Labbe the arytenoid exfoliated, was inspired, and caused death. A formed sequestrum may be buried for years. When cicatrization occurs, stenosis almost invariably follows. The gummatous form of laryngeal syphilis may persist for months or even years before ulceration appears. The necrosis is at first evident near the center and gradually extends until the gummatous tissue is removed. If treatment be instituted early, ulceration may be escaped. Cicatrization of the tertiary lesions of syphilis is commonly followed by intractable contraction, giving rise to stenosis (syphilitic stricture of the larynx). Syphilis of the

[1] See Robertson, "Jour. Amer. Med. Assoc.," Jan. 17, 1903; p. 163. Conner, "Amer. Jour. of Med. Sci.," July, 1903. Chauffard and Viollet, "Gaz. des Hôp. Civils et Mil.," June 9, 1904.

trachea is less common than in the larynx; laryngeal and tracheal syphilis are rarely associated with pulmonary manifestations, while in protracted cases of tuberculosis the lungs never escape. Nicholson[1] reports an instance in which a gumma adjacent to the trachea communicated with the aorta, and later, by rupture, gave rise to a fatal tracheal hemorrhage.

Leprosy, actinomycosis, and **rhinoscleroma** rarely affect the larynx and trachea. Paratracheal and laryngeal lesions, in any of these conditions, may extend and involve the structures named.

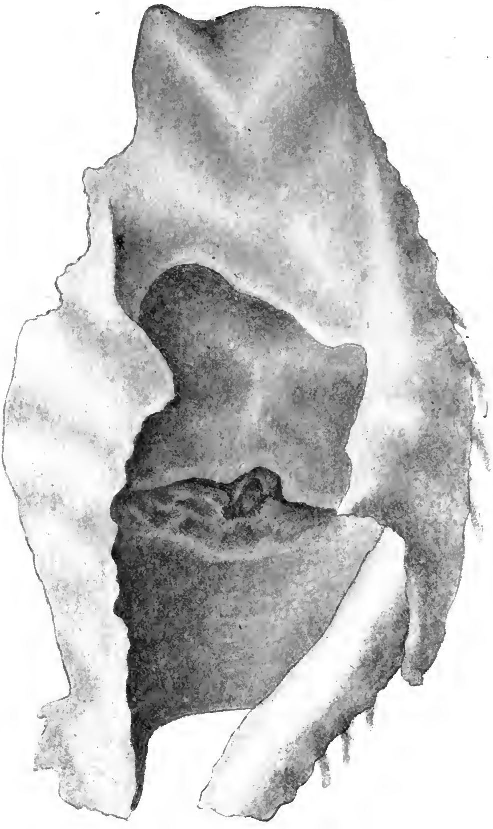


FIG. 285.—PERICHONDRITIS, NECROSIS, AND LARYNGEAL ULCERATION.—(*Specimen from patient dead of typhoid fever.*)
The area shown near the center indicates the outline of an ulcer, the floor of which was smooth and healing. Near the center is seen a black necrotic mass of exfoliating cartilage.

Perichondritis is, as its name indicates, an inflammation of the perichondrium. It is usually secondary to acute inflammations of the overlying mucosa; less frequently it results from extension of an infectious process from the contiguous tissues. The condition is rarely primary, commonly following tuberculosis, syphilis, and the more acute infectious diseases, such as typhoid and typhus fevers, smallpox, etc. Tubes left in the trachea, probably by continuous irritation, may give rise to inflammation of the perichondrium. Pus forms in the perichondrium, escapes through the submucosa and mucosa, and an ulcer follows in which exfoliation of the cartilage takes place; the necrosed cartilage falls into the larynx and is expectorated, or it may, acting as a foreign body, reach a bronchus, or, lodging in the air-passage at any point, may give rise to acute obstruction. After exfoliation, in non-tuberculous cases, the ulcer tends to heal. In both tuberculosis and syphilis separation of the necrotic tissue is often slow and may be delayed for months; it is also possible for a small area of necrotic cartilage to be healed in and remain quiescent during a long period, or even indefinitely.

[1] "Lancet," Aug. 2, 1902, p. 293.

Calcification of the cartilages is seen in the old, rarely in the young or middle-aged.

Edema[1] of the glottis may be acute or chronic. The acute form is practically always inflammatory and may be due to the pneumococcus, streptococcus, pyogenic staphylococci, and, although less commonly, to a few other bacteria. Straussler and others have described instances of acute circumscribed edema, involving the larynx and thought to be of neuropathic origin, resembling the nodular edemas of the skin described by Quincke. It is generally conceded that acute primary **œdema laryngis** is an infection by some of the bacteria already mentioned. In some cases the exudative fluid is serous (**serous edema**), and in other instances the change resembles diffuse suppuration (**phlegmonous edema**). Either of these may result from inflammation of the overlying mucosa or adjacent tissues. Definite suppuration, in the sense that macroscopic pus is present, rarely occurs. Chronic forms of edema of a mild degree may suddenly manifest the characters of an acute inflammatory edema.

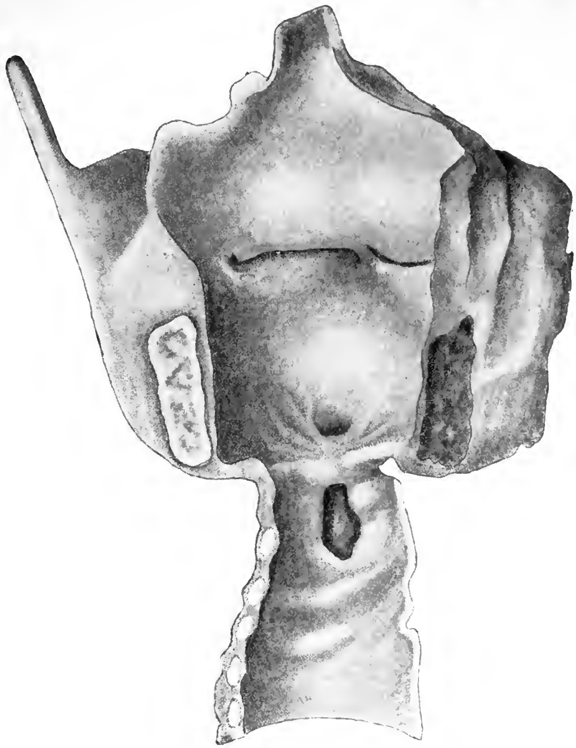


FIG. 286.—TRACHEAL AND PARTIAL LARYNGEAL STENOSIS FOLLOWING CICATRIZATION OF A GUMMA.

The syphilitic lesion has evidently destroyed parts of two tracheal rings, and extended upward into the larynx. The cartilage on the right shows results of a slowly progressing perichondritis, with beginning necrosis although the overlying mucous membrane is not involved.

Chronic edema of the larynx may follow or precede the acute form or may arise independently, the latter being by far the more common. It may occur as a result of the venous distention seen in valvular heart disease, and compression of the veins returning from the larynx by tumors, cysts, goiter, etc. Pulmonary emphysema, dropsical affections associated with kidney diseases, or obstructive heart lesions may terminate fatally by an attack of edema of the glottis; chronic infectious processes in the vicinity are not infrequently attended by a mild degree of edema. In either form edema may threaten life by occlu-

[1] Straussler, "Prag. med. Woch.," Nov. 12, 1903. Rice, "N. Y. Med. Jour.," Dec. 3, 1898, p. 813.

sion of the passage, giving rise to a condition called *inflammatory stenosis of the larynx.*

Laryngeal stenosis, exclusive of the malformations, occurs in two forms—(1) functional and (2) organic. *Functional* **stenosis of the larynx** results from paralysis of the muscles that open, or from spasms of those that close it. The former commonly follows faulty innervation, due to central disease of the nerve-trunks, or brain, or is secondary to pressure on the nerves by tumors, aneurysms, etc. That paralysis may follow degeneration of the muscle without antecedent nerve change seems doubtful. **Organic stenosis of the larynx** follows contraction in healing ulcers, notably the syphilitic ulcerations; laryngeal tumors, edema, and inflammations; pressure from without, as by tumors and enlargements of the surrounding glands, and aneurysm. The lumen may be narrowed as the result of hemorrhage into the mucosa, fracture or other injury to the laryngeal structures, as in throttling. Laryngeal obstruction depending upon the presence of false membrane, congenital hypoplasia, and foreign bodies is not correctly considered among the stenoses, although the influence upon respiration is practically the same.

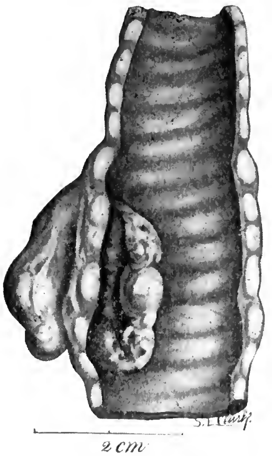


FIG. 287.—TRACHEA OF CHILD (AGE ELEVEN YEARS) SHOWING CARCINOMA EXTENDING THROUGH THE WALL AS AN IRREGULAR EXTERNAL MASS.

The trachea is markedly dilated at the level of the new growth. (I am indebted to Dr. Sappington for the loan of the specimen from which this drawing was made.)

Tumors of the Larynx.[1]—*Adult Epithelial.*—*Papillomata* are by far the most common. They may consist of fibrous as well as epithelial increase in the papilla, and may be soft and dendritic, or pachydermatous and dense from the thickening and subsequent hardening. In some cases multiple papillomata occur; they are usually small, often vascular, and are sometimes pedunculated. Papilloma usually arises on or near the vocal cord and anterior portions of the larynx, and in some cases the tumors are irregularly distributed over the whole laryngeal mucosa. Sometimes the histologic resemblance to cancer is striking, rendering the microscopic diagnosis most difficult. All forms of papilloma are likely to undergo transformation into cancer.

Cancers of the larynx are usually epitheliomata; 248 of 486 cases were of the squamous type. Since Krishaber made the division into intrinsic and extrinsic, systematic writers have generally accepted the two forms. The *intrinsic laryngeal cancer* originates from the true or false vocal cords, the mucosa of the ventricles, or less frequently lower in the organ. Sendziak found but 5 subglottic in 486 cases of laryngeal cancer. The *extrinsic cancer* arises from the epiglottis or other parts

[1] Haring, "Brit. Med. Jour.," Sept. 28, 1901. Gleitsmann, "Med. Record," July 5, 1902. Harmer, "Wien. klin. Woch.," Jahrg. XV, June 12 and 19, 1902. Fein, 'Wien. klin. Woch.," July 10, 1902. Von Bruns, "Beitr. z. klin. Chir.," lxi, Nos. 1 and 2. Terry, "Annals of Surgery," June, 1904, p. 968. de Santi, "Lancet," June 18, 1904, p. 1710. Culbert, "Amer. Med.," July 9, 1904. Semon, "Lancet," Nov. 5, 1904, p. 1263. Rosenheim and Warfield, "Amer. Jour of Med. Sci.," June, 1904, p. 1045.

of the pharynx or contiguous tissue; it is very much less frequent than the intrinsic, and, in the larynx, does not extend with such rapidity. Papillomata occur in childhood and in adolescence; cancer in middle life or later. In rare instances papilloma accompanies or may even follow carcinoma; the association of the two neoplasms often gives rise to errors in diagnosis. Particles excised for examination are likely to be papillomatous, and hence the underlying cancer is overlooked.

Connective-tissue tumors of the larynx are not frequent. Harmer and also Fein have reported instances of **lymphangioma. Fibrous polypi,** which may be hard or soft, have occasionally been observed. **Laryngeal myxoma** and **chondroma** are rare tumors. **Sarcoma** of the larynx is occasionally observed.

Tumors of the trachea are exceedingly rare; Schmidt observed 7 in 3120 tumors of the upper respiratory tract. The malignant growths may be primary or secondary, usually the latter. In an analysis of all the recorded cases of tracheal tumor Rosenheim and Warfield found that 34 were papillomata, 33 carcinomata, 30 chondromata and chondro-osteomata, 23 fibromata, and 22 sarcomata. Thyroid tumors (**intra-tracheal goiter** or **struma**) sometimes arise in the larynx or trachea and are due to ectopic islands of thyroid gland. Bruns reports 5 such growths and has been able to collect 6 from literature; frequently they show no anatomic connection with the thyroid gland; occasionally such masses become cancerous. Bruns has operated on a malignant intra-tracheal struma.

BRONCHI.

Normal Structure.—The bronchi consist of a series of tubes lined by columnar epithelium, which is ciliated down to the terminal branches, in which it becomes cuboid and loses the cilia; the wall of the bronchus, in addition to the cartilaginous rings, is composed of fibrous and elastic tissue and of a small quantity of unstriped muscle, the latter being most abundant between the ends of the incompletely encircling cartilage. The mucous membrane of the larger bronchi contains numerous mucous glands.

Malformations.—When arrest of development has occurred previous to the structural completion of the lung, the bronchi may terminate as blind pouches or may be absent. Congenital narrowing or the reverse may be found. (See Bronchiectasis, p. 579.)

Hyperemia and congestion manifest themselves under the same conditions and induce changes similar to those already described when considering the larynx and trachea.

Hemorrhage.—(See Hemoptysis, p. 584.)

Catarrhal bronchitis, both acute and chronic, is one of the most frequent diseases of the bronchi.

The investigations of Ritchie[1] clearly establish that there is no specific organism for bronchitis, but that the condition may result from infection by pneumococci, streptococci, and occasionally staphylococci; in many cases it is polymicrobic. When accompanying grippe, it is due to the Bacillus influenzæ,[2] and occasionally is caused by the same organ-

[1] "Jour. of Path. and Bact.," 1902, vol. vii, No. i.
[2] See p. 126.

ism, and unaccompanied by the other symptoms of influenza. Bronchitis frequently affects children and the aged. Sill[1] states that 293 of 1000 sick children suffered from some form of bronchial inflammation. In both extremes of life sudden temperature variations, and possibly also barometric changes, seem to bear a definite relation to the occurrence of the attack. Bronchial catarrh to some degree accompanies practically all infections in which inflammation affects the upper air-passages; it is, therefore, common in diphtheria, scarlet fever, and particularly measles, and often develops during pertussis.

Morbid Anatomy.—The changes observed in the bronchial mucosa are those usually present in acute catarrhal inflammations of a mucous membrane.[2] Lemoine[3] states that in an epidemic of grippe he observed 18 cases that corresponded to the type of bronchitis which has been called **suffocative bronchial catarrh.** The pathology of this manifestation is still a matter of doubt, but the clinical features indicate that the intense asphyxial symptoms are due to an unusual degree of submucous swelling, and consequent narrowing of the affected tubes. Bronchial infections frequently extend into the vesicular structures, giving rise to lobular pneumonia. In the larger tubes the glands of the mucosa may stand out prominently, constituting a *follicular bronchitis.* When the inflammatory products are abundant, clear, serous fluids, the name **bronchorrhea** is given; *bronchoblennorrhea* is applied to the condition when a puriform expectoration is present. These probably represent different stages in the same inflammatory process. **Putrid or fetid bronchitis** is due to decomposition of the bronchial secretion by saprophytic bacteria; it is usually associated with bronchiectasis, the dilated cavities affording storage sufficient to permit the development

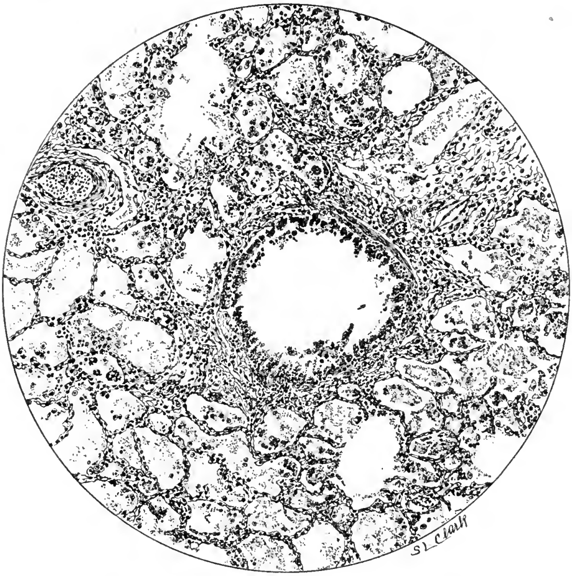


FIG. 288.—LUNG, INCLUDING A SMALL BRONCHUS. BRONCHITIS AND BEGINNING LOBULAR OR BRONCHOPNEUMONIA.

The bronchus (center of field) shows desquamation of epithelium, many of the cells being completely detached and others in process of detachment. The bronchial wall is infiltrated by mononuclear leukocytes. Many of the adjacent air vesicles contain a granular deposit resulting from precipitation, during fixation, of an albuminous exudate; in this granular material are varying numbers of mononuclear cells and epithelial cells, the latter having been shed from the alveolar walls.

[1] "N. Y. Med. Jour.," Feb. 6, 1904, p. 253.
[2] See Inflammations of the Mucous Membranes, p. 546.
[3] "Soc. méd. des Hôp.," March 5, 1905.

of decomposition. Similar facilities are present in pulmonary gangrene, in empyema with perforation of a bronchus, in tuberculous cavities, etc. By some the condition is attributed to a specific organism; by others, to the colon bacillus. Actinomyces, oidium albicans, aerobic bacteria of decomposition, and possibly other organisms may be active in producing the accompanying fetor.

Chronic catarrhal bronchitis is usually a sequence of repeated attacks of the acute form. The persistence of the bronchial catarrh is favored by systemic vices that disturb nutrition or excretion or both the bronchial inflammation accompanying gout, nephritis, and diabetes belongs with this group. A bronchitis of varying intensity usually accompanies the chronic pulmonary congestion of uncompensated heart disease,[1] and is often a part of chronic interstitial pneumonia emphysema, and the interstitial changes associated with pneumoconiosis. When the bronchial inflammation has persisted for any length of time, there is always a tendency toward the development of fibrous tissue around the bronchi—the **peribronchitis chronica** of German writers. In some cases atrophic changes occur in the mucosa, converting the moist mucous, or mucopurulent, form into the dry catarrh. (See Fig. 273, p. 549.) Chronic bronchitis is a recognized cause of bronchiectasis. The relation of emphysema to chronic bronchial disease will be considered later. Fränkel[2] describes a form of bronchitis affecting particularly the smaller bronchi (**bronchiolitis**), attended by marked fibrous induration in the pulmonary tissue and obliterating changes in the bronchioles.

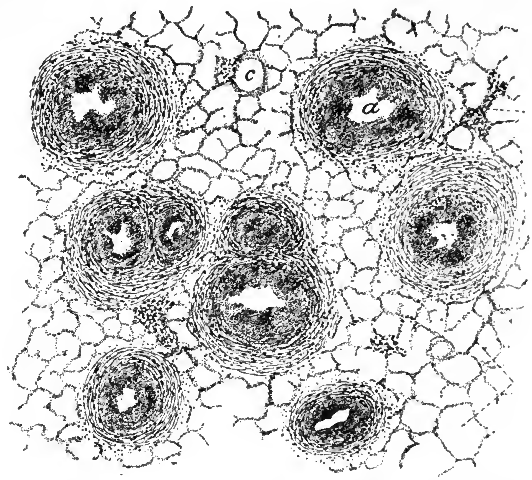


Fig. 289.—Chronic Caseous Bronchitis, Tuberculous Bronchitis, Caseous Softening of the Bronchial Wall, with Thickening of the Peribronchial Tissue, Peribronchitis Chronica.—(*Schmaus*.)

a. Bronchus with thickened and caseous wall surrounded by a layer of fibrinous tissue. Several other bronchi are shown, but representing slightly different degrees of the process. *b*. Transverse section of interlobular septum. *c*. Blood-vessel.

Fibrinous[3] or **pseudomembranous inflammations of the bronchi** may be acute or chronic. **Acute fibrinous bronchitis** is usually due to the diphtheria bacillus and frequently accompanies diphtheria, particularly the laryngeal form. It may also be caused by the pneumococcus and

[1] See Brown Induration of the Lung in Chronic Heart Disease, p. 519.

[2] "Deut. Arch. f. klin. Med.," 1901, Bd. 73.

[3] Hochhaus, "Deut. Arch. f. klin. Med.," vol. lxxiv, Nos. 1 and 2. Chaplin, "Hunterian Society," Nov. 26, 1902, also "Lancet," Dec. 13, 1902, p. 1630. Liebermeister, "Deut. Arch. f. klin. Med.," 1904, vol. 80, Nos. 5 and 6. Lange, "Deut. Arch. f. klin. Med.," vol. 79, H. 3 and 4. Finckh, "Beitr. z. klin. Chir.," vol. xli, No. 3.

less frequently by staphylococci. With regard to the conditions giving rise to **chronic fibrinous bronchitis** we are less fully informed. Finckh describes a pseudomembranous bronchitis accompanying pulmonary actinomycosis, and it is well known that false membrane in the bronchi may be a manifestation of chronic tuberculosis. Lange reports the occurrence of a type of bronchial lesion manifested by the presence of homogeneous plugs in the bronchioles sometimes extending into the alveoli and containing no demonstrable bacteria.

Morbid Anatomy.—In both the acute and chronic forms of fibrinous bronchitis casts are often expectorated; they may be fragmentary or represent a relatively large bronchial tree. The medium sized and larger portions of the casts usually possess lumina that can be recognized in the gross specimen. Smaller casts may be solid. Liebermeister has shown that they contain fibrin and that mucus may be present.[1]

Gangrenous and **hemorrhagic inflammations of the bronchi** are rare, and follow or accompany pulmonary gangrene, the inspiration of powerful irritants, and the presence of foreign bodies. Such lesions are occasionally observed in pyemia and other septic manifestations, and sometimes are secondary to extensions from empyema.

Suppurative peribronchial lymphangitis is an inflammation of the lymphatics surrounding the bronchi. The condition may follow pleurisy, —more especially the suppurative form (empyema),—abscess, gangrene, septicemia, pyemia, and allied infectious diseases. It is not recognizable during life, and postmortem is manifested by a purulent infiltration of the peribronchial tissues, at times extending to the lymphatic nodes; if not due to, it is usually followed by, septicemia or pyemia.[2]

Tuberculosis of the bronchi is usually secondary to a pulmonary lesion. Commonly it accompanies the chronic caseous tuberculosis, although in the acute miliary form tubercles in the submucosa of the bronchus may be observed. **Chronic caseous bronchitis** or **peribronchitis** is a manifestation of tuberculosis. In the **actinomycotic peribronchitis** transverse sections of recent lesions usually reveal the fungous granules.[3] According to Fütterer,[4] the new tissue in the submucosa and adjacent structures possesses a sulphur-like hue and lung involvement occurs late. **Syphilitic bronchitis** and **peribronchitis** are rare occurrences and are usually due to an associated syphilitic interstitial pneumonia.

Pigmentary infiltration[5] of the bronchial mucosa and the effects of congestion have been studied.

Stenosis of the bronchi may be due to swelling of the mucosa (bronchial turgescence, such as occurs in bronchial asthma); to occlusion, more or less complete, by fibrinous exudate or mucus; to pressure from peribronchial exudates, as in tuberculosis, or to contraction of newly formed cicatricial tissue, as in syphilis; to intrabronchial tumors; or to pressure from neoplasms of the lung or peribronchial lymph-nodes

[1] The structure and development of these casts are discussed on p. 551.
[2] See Pulmonary Suppuration, p. 592.
[3] See p. 167.
[4] "N. Y. Med. Jour.," Aug. 24, 1901.
[5] See Infiltrations of the Mucous Membranes, p. 542; also Pigmentary Infiltrations, p. 231.

or from aortic aneurysms, mediastinal tumors, and neoplasms of the esophagus. Foreign bodies may obstruct or occlude the bronchi. Atelectasis and atrophic or inflammatory changes occur in the lung tissue beyond the point of stenosis, while bronchiectasis may develop in the bronchus on the trachea side of the obstruction.

Asthma[1] has been attributed to (1) hyperemia and (2) swelling of the mucosa of the smaller bronchioles, and (3) to an exudative bronchiolitis. The recent studies of Brodie and Dixon indicate that the anatomic basis of acute asthma is spasm of the smaller bronchi.

Bronchiectasis,[2] or dilatation of a bronchus, occurs in two forms —(1) *congenital* and (2) *acquired*. (1) **Congenital bronchiectasis** is unilateral, usually general, affecting many or all of the bronchi of that side (*bronchiectasis universalis*, Grawitz). The condition is a tubular or cylindric dilatation of the bronchial tubes. It is very rare, and the cause is but poorly understood. (2) **Acquired bronchiectasis** arises as the result of chronic bronchial inflammation, interstitial pneumonia, atelectasis, adhesions of the pleura, tuberculosis, peribronchial inflammations, usually tuberculous, or accumulated bronchial secretions. Foreign bodies in the bronchi and tumors may also be causes. Two conditions are necessary in bronchiectasis: (1) Some lesion leading to softening of the bronchial wall; (2) a distending force. All the foregoing offer these, and any conditions inducing them may bring about dilatation. The inflammatory conditions soften the walls, and the attending cough offers the distending force; where an area of the lung is collapsed, the bronchus delivering air to that part is subjected to inspiratory distention, and commonly dilates. A number of observers have described a form of bronchiectasis involving the bronchioles, and hence called **bronchiolectasis.** The condition is said to develop acutely, and hence is termed acute bronchiectasis, or bronchiolectasis.

As a rule, the bronchiectatic cavities are fairly evenly distributed within the lung. In over fifty per cent. of the cases but one lung is involved. Any part of the lung may contain dilated bronchi, but apparently they are most frequent in the lower and middle lobes. Statements to the contrary probably arise from failure to differentiate the cavities of tuberculosis from those due to bronchiectasis.

The *bronchiectatic cavity* may be uniform, cylindric, or tubular, as in the bronchiectasis universale; fusiform, or spindle-shaped, saccular, globular, or irregular in outline; the last is found in bronchiectasis due to interstitial pneumonia. As one part of the bronchial wall is nearly always weaker than some other point, the cavity is rarely symmetric. The cavity of a dilat-d bronchus may be eight centimeters, or even larger, in diameter, and from that size down to an almost inappreciable dilatation. The cavity may be differentiated from those due

[1] "Trans. of Path. Soc. of London," 1903, vol. liv, Part i.

[2] Ackland, "Practitioner," April, 1902. Criegern, "Ueber akute Bronchiektasie," Leipzig, 1903. Hondo, "Centralbl. f. allg. Path. u. path. Anat.," 1904, No. 3, p. 129. Edens, "Deut. Arch. f. klin. Med.," 1904, Bd. 81, H. 3 and 4. James, "Brit. Med. Jour.," Jan. 2, 1904, p. 5. Siewert, "Berl. klin. Woch.," Feb. 8, 1904. Jochmann and Moltrecht, "Ziegler's Beitr.," 1904, Bd. 36, H. 2. Tuffier, "Bull. et Mem. de la Soc. méd des Hôp. de Paris," 1899 and 1900, also "Comp. Rend., Sect. de Path. XIIIme Cong. Internat.," Paris, 1901. King, "Jour. of Path. and Bact.," July, 1904, p. 471. King, "Scottish Med. and Surg. Jour.," June, 1904.

to tuberculosis by the following points: In bronchiectasis the wall may be smooth and lined with epithelium, and may contain, at points, if not throughout, remnants of the normal bronchial wall; if the cavity be roughened by ulceration, it is at the most dependent point. The points of entrance and exit of the bronchus may be seen. No shreds of blood-vessels or of other bronchi or bronchioles are to be seen in the wall or extending into the cavity. Recognition of the cause may aid in differentiation. The absence of tubercle bacilli and of anatomic tubercles in the wall, of course, excludes tuberculosis.

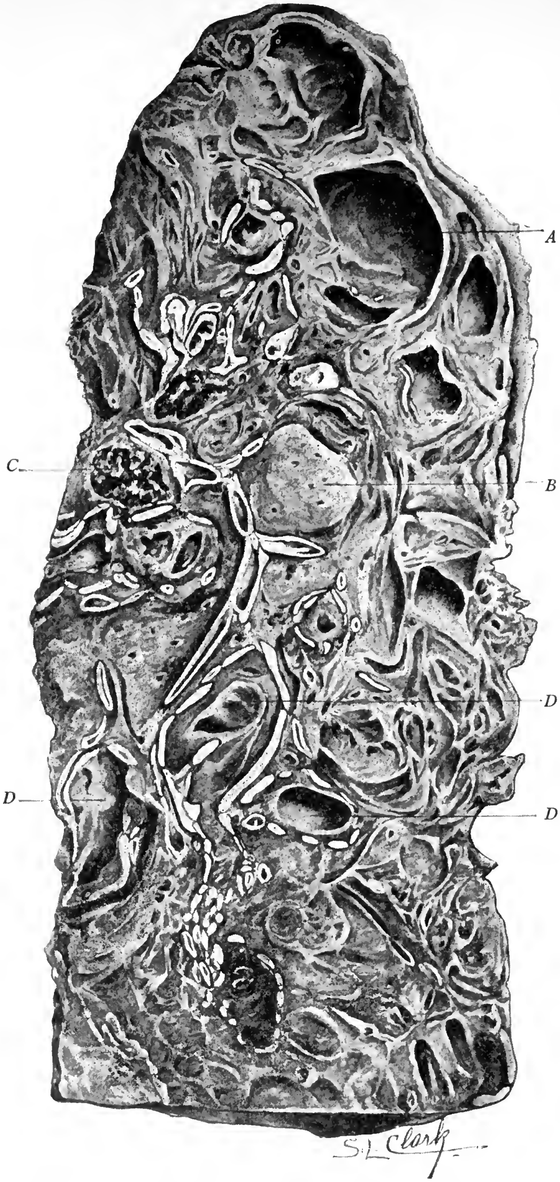


FIG. 290.—LUNG, EMPHYSEMA AND BRONCHIECTASIS. (Natural size.) *A*. Emphysema vesicle. *B*. Enlarged peribronchial gland. *C*. Enlarged peribronchial gland, pigmented. *D*, *D*, *D*. Dilated bronchi.

The cavity often contains accumulated secretion, and this is frequently fetid, owing to saprophytic infection and decomposition. Ulceration may open the peribronchial lymphatics and infection of the contiguous tissue may ensue, giving rise to pulmonary abscess or to gangrene.

Tumors of the bronchi, as primary growths, are exceedingly rare.

Bronchioliths,[1] so called, rarely arise in the bronchi, although it is possible that inspissated secretion might calcify if retained sufficiently long. Concretions of this kind usually result from calcified

[1] Stern, "Deut. med. Woch.," 1904, xxx, No. 39 1414. Atlee, "Amer. Jour. of Med. Sci.," July, 1901.

tuberculous areas or glands which erode into the bronchi. The expectoration of lung stones is usually associated with pulmonary excavation, and has been called **lithogenous phthisis.** In the case reported by Stern the patient coughed up at least twenty such calculi. Some of these bodies are parts of exfoliated cartilage, and it is probable that all containing true bone possess this origin. Chemically, broncholiths are composed of carbonate and phosphate of lime.

LUNGS.

Normal Structure.—The bronchi, by dichotomous division, eventually terminate in the infundibula, around which are arranged the air vesicles. The ciliated epithelial cells lining the bronchi become low, nonciliated, and eventually polygonal cells, which, in turn, are transformed into flat, pavement-like cells in the air-vesicle. The wall of the air vesicle is composed of fibrous and elastic tissue, in which ramify the capillaries derived from the pulmonary artery. The nutrition is dependent upon the bronchial circulation. The normal weight of the lungs is subject to wide variations because, no matter what condition has given rise to death, the slow circulation of the agonal period gives rise to an increased amount of blood and serum in the pulmonary tissues. It is usually stated that the left lung, which is the lighter, weighs from 300 gm. to 450 gm., and the right lung from 350 gm. to 550 gm. The studies of Spitzka[1] on the lungs of criminals executed by electricity show that the normal left lung weighs from 216 gm. to 280 gm., and the right from 240 gm. to 350 gm.

Malposition of the lung may be congenital or acquired; a lung that has never expanded lies near the median line posteriorly and so occupies a position that is essentially normal. In eventration of the diaphragm[2] the lung on the affected side is usually unexpanded and displaced toward the apex of the pleural cavity. **Acquired malposition of the lung** results from altered pressure relations within the thoracic cavity and abnormal openings in the wall. The most important of the pulmonary malpositions are the **hernias of the lung.** Wounds in the thoracic wall may permit a lobe or part of a lobe to escape the chest cavity. When fenestra, or wounds, involve the diaphragm, usually an abdominal viscus enters the thoracic cavity; only rarely is the hernia in the opposite direction. A number of observers[3] have shown that it is possible for pulmonary hernia to occur without wounds in the chest wall. The apex of the lung may rise in the neck to an abnormal height, and in rare cases a true cervical or supraclavicular hernia may occur.

Malformation[4] of the lung is infrequent. Absence of a whole lung

[1] "Proceed. of the Assoc. of Amer. Anatomists," 1903, p. 5.

[2] This condition is briefly described on p. 485; see also, Doering, "Deut. Arch. f. klin. Med.,," 1901, Bd. 72, H. 5 and 6. Glaser, "Deut. Arch. f. klin. Med.," 1903, H. 3 and 4.

[3] Reibold, "Münch. med. Woch.," March 8, 1904, p. 433. Bickel, "Deut. Arch. f. klin. Med.," Bd. 78.

[4] Springer, "Prager med. Woch.," Aug. 4, 1898. Hanson, "Jour. Amer. Med. Assoc.," Sept. 14, 1901, p. 701. Neisser, "Zeit. f. klin. Med.," vol. xlii. Lewisohn, "Centralbl. f. allg. Path. u. path. Anat.," Nov. 15, 1903. Humbert, "Revue de Méd.," 1904, vol. 24. Oberwarth, "Mittheilungen a. d. Grenzge-

or a part of a lung, occasionally occurs; absence of both lungs has been observed. Additional lobes (*multilobulated lung*) have been found present in numerous instances. Aberrant lobes, or even a miniature lung unconnected with any normal or patulous air-passage, have been observed. Hypoplastic or underdeveloped lobules or rarely lobes have been found, and the reverse may occur. Arrest of development involving part of a lung, or it may be all of one lung, is usually associated with the corresponding overdistention of the developed portion of the affected organ, or opposite lung, constituting a compensatory emphysema. (See Emphysema.)

Hyperemia (active congestion or active hyperemia of some writers) occurs in violent exercise, in the initial stage of acute inflammations of the lungs or pleuræ, in the chill or cold stage of malarial and septic paroxysms, and in allied conditions that incite powerful cardiac action excessive heat or cold is also said to favor hyperemia. It is asserted that pulmonary hyperemia precedes death from disease of the coronary arteries; disease and injury of the pons or medulla are possible causes. Localized hyperemia occurs around diseased areas that interfere with the circulation, such as infarcts, circumscribed catarrhal or croupous pneumonia, and areas invaded by any of the chronic infectious diseases to which the lung is liable.

If the lesion be purely a hyperemia, the condition to be noted in the initial stage of fibrinous pneumonia will be found.

Congestion (passive hyperemia or passive congestion of some writers) is dependent upon slowing of the pulmonary circulation from (1) deficient force from the right heart; (2) from non-aeration of the lung; (3) from increased tension in the pulmonary veins, usually due to impeded progress in the left heart, as in valvular disease of the mitral orifice, associated with obstruction or regurgitation. In the vast majority of cases more than one of these causes will be found acting. Two forms of pulmonary congestion are constantly observed—(1) *brown induration* and (2) *hypostatic congestion*. Brown induration has already been described. (See p. 519.) It results from disease of the left heart most commonly, but may be brought about when any obstacle beyond the pulmonary capillaries impedes the circulation. Pulmonary edema is frequently associated with chronic congestion.

Hypostatic congestion arises as the result of weakened heart action, deficient respiration, and the influence of gravity. It is found in febrile conditions (*e. g.*, typhoid fever), in the aged, and after prolonged stay in the recumbent posture, as when a fractured limb is treated with the patient prone.

This form of congestion has also been observed in morphin-poisoning and in association with, or following, disease and injuries of the brain; in the latter case the condition is further favored by deficient movement or innervation of the side affected, and is usually most marked when paralysis is present. All forms of coma favor the development of hypostatic congestion.

Being influenced by gravity, the dependent parts of the lung are

bieten d. Med. u. Chir.," 1904, Bd. 13, H. 4 and 5; also "Jahrbuch f. Kinderheilkunde," 1904, Bd. 60. Hammer, "Zieg. Beitr.," 1904, Bd. 36, H. 3. Couvelaire, "Revue Mens. des Mal. l'Enfants," Feb., 1904. Otto, Inaug. Diss. München, 1904.

principally involved. The affected area is dark in color, often almost black, much heavier than normal, pits on pressure, and when incised, blood or bloody serum streams from the cut surface. The blood may be retained in the vessels and the serum in the intervesicular structure, in which case the affected area floats in water; not uncommonly however, the serum and even some blood permeate the vesicular wall and penetrate the air alveolus, in which case areas may be selected which sink in water. This latter condition has been called splenization and **hypostatic pneumonia.** When hemorrhage or infiltration of blood occurs in the vesicular wall, the changes observed may resemble those seen in diffuse pulmonary apoplexy.

The gross anatomy, as just given, indicates the histology. In poorly marked cases, after hardening, very slight histologic changes may be evident; a few leukocytes and mucous cells in excess are present in the vesicles; the vesicular epithelium is found cloudy and often desquamating. In more marked cases, in addition to the foregoing, the vesicles contain more or less blood, and infiltration of the pulmonary connective tissue by serum and blood may be demonstrable.

Pulmonary edema[1] may be general or local, acute or chronic. The acute may be further divided into the acute simple and the acute fulminating. **Acute fulminating pulmonary edema** appears suddenly, sometimes when the previous health has given no warning. Arteriosclerosis is usually present in this as in other forms of edema of the lung, and in most cases there is also a chronic interstitial nephritis. Brouardel does not recall having seen a case of pulmonary edema without renal lesions; Allbutt has noted its association with aortitis. The condition may be produced experimentally by the administration of adrenalin. This hyperacute form may run its course and terminate fatally within an hour. At the autopsy the lungs are found hyperemic, in areas inundated, and the bronchi filled with a reddish, frothy mucus. Should the patient survive a single attack, recurrences are not infrequent. The patient reported by Lissaman had seventy-two attacks in two and a half years; during one attack 1260 c.c. of fluid was expectorated in eight hours. The **simple acute pulmonary edema** appears with less rapidity and is rarely so intense. The bronchial contents and sputum are not so red, although the quantity of albumin is usually greater. It occurs especially in connection with pulmonary congestion, nephritis, arteriosclerosis, and cardiac failure. It may accompany violent septic processes and pulmonary embolism. Anatomically the lung is the seat of changes essentially similar to those in the next form to be described. **Chronic pulmonary edema** is observed in Bright's disease, particularly chronic parenchymatous nephritis. It may also be caused by chronic pulmonary congestion, profound anemias, mediastinal tumors,

[1] The principal data concerning pulmonary edema can be obtained from the following references: Meltzer, Harrington Lectures, University of Buffalo, 1904; also "Amer. Med.," July 2, 9, 23, and 30, 1904. Owen, "Brit. Med. Jour.," Jan. 2, 1904, p. 1. Blumer, "Albany Med. Annals," Aug., 1901. Steven, "Lancet," Jan. 11, 1902. Rowland, "Lancet," Jan. 25, 1902. Lissaman, "Lancet," Feb. 8, 1902. Riesman, "Amer. Jour. of Med. Sci.," April, 1902. Crummer, "Northwestern Lancet," June 1, 1902. Merklen, "La Méd. Moderne," May 13, 1903, p. 145. Hewlett, "Intercolon. Med. Jour.," Dec. 22, 1903, p. 611. von Rieckhoff, Inaug. Diss., München, 1904. Josué, "La Presse Méd.," Jan. 21, 1905 p. 41.

and in any condition in which the death agony is prolonged. The pulmonary edema associated with albuminous expectoration and following thoracocentesis, usually resembles the acute simple form of edema of the lungs, but may possess some of the characters of the chronic form. Chronic pulmonary edema is usually held to be the result of increased tension in the capillaries of the lung, associated with changes in the endothelium. There is a growing belief that it may be due to infection; Blumer has found that such lungs frequently contain bacteria.

Morbid Anatomy.—In marked cases the whole lung is affected, but all parts are not involved to the same degree; the lesion is most intense in the dependent areas. The lung pits on pressure, does not always crepitate throughout, is often boggy, and is always more succulent than normal. In the absence of hyperemia the organ is pale, but, as the blood-content is nearly always increased, the color is commonly dark. As soon as incised, serum, which is usually blood-stained and frothy, streams from the cut surface. The greatly increased weight is clearly due to the large amount of serum and excess of blood in the organ; usually the lung crepitates throughout, but in marked cases selected areas may be airless. In such cases the air-vesicles may be filled by transuded serum, or it is possible that serum in the bronchi may be aspirated into and fill the lobules. It is rare for large areas to be solidified. Microscopically the vascular distention is often slight, but may be marked. The interstitial tissues are separated and many of the air-vesicles contain serum and a few cells (Plate XIII). In the absence of infarction red cells are never abundant in the alveoli. There is nearly always more or less evidence of bronchitis, which is catarrhal in type. Sometimes at autopsy the lungs are gelatinous and trembling, and in such cases I have found a small amount of fibrin which may be an evidence of postmortem coagulation of the edema fluid.

Localized pulmonary edema occurs around neoplasms, infarcts, and acute inflammatory and tuberculous areas in the lung. The condition is sometimes called collateral, circumscribed, or focal edema, and is always determined by some local lesion.

Hemoptysis, also called blood-spitting, bronchopulmonary hemorrhage, or simply pulmonary hemorrhage, may be due to falls, blows upon the chest, wounds of the lung or bronchi, or other forms of trauma. The most common cause is tuberculosis, in which condition the hemorrhage may be due to miliary or ulcerative lesions of the air-passages, or the rupture of vessels, whether aneurysmal or not, in cavities. Weismayr[1] strongly urges the older belief that most of the hemorrhages are due to aneurysms in caseous cavities. Any form of laryngeal, tracheal, or bronchial ulceration in which a bronchial artery is opened may be a cause. Bronchiectasis rarely gives rise to hemoptysis. In pulmonary congestion, such as accompanies heart disease, and in hyperemia of beginning pulmonary inflammation, slight hemorrhages sometimes occur. In malignant tumors of the lung, or tumors involving the bronchi, trachea, or larynx, hemoptysis is occasionally observed. Leprosy and actinomycosis may be mentioned among the rare causes. Pulmonary abscess and, especially, gangrene of the lung often give rise to bleeding which may be fatal. Aneurysm of the pulmonary

[1] "Wien. klin. Rundschau," April 20, 1902.

PLATE XIII.

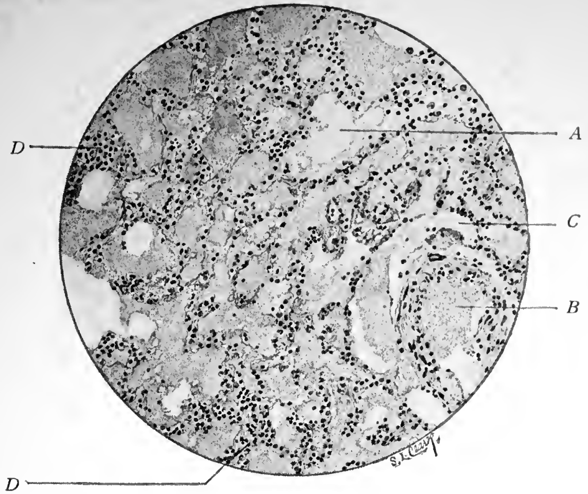


FIG. 1.
LUNG, EXPERIMENTAL (ADRENALIN) EDEMA.

A. Air vesicle, practically empty. *B*. Artery containing a granular thrombus. *C*. Lymphatic, partly occupied by granular material. *D*, *D*. Intervesicular septa, the connective tissue substance of which is dissociated; in some areas an infiltration by mono-nuclear cells is also present. Such elements are particularly abundant at the points indicated by the leaders from *D*.

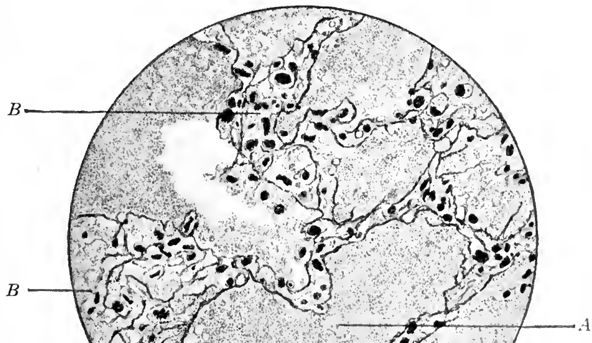


FIG. 2.
LUNG OF RABBIT, EXPERIMENTAL (ADRENALIN) EDEMA.
(Zeiss, 2 mm. obj., proj. ocular; reduced one-half.)

The alveoli are practically filled with a granular material that is stained by acid dyes. The intervesicular septa are swollen, and at points conspicuous separation of the fibrous and elastic tissues is present. *A*. Air vesicle containing granular material; other vesicles are also shown. *B*, *B*. Swollen septa; the finely granular material in the interstitial tissue is evidently the result of precipitation o proteids by the fixing agents.

artery or its branches, of the aorta, innominate, internal carotid, or even the subclavian, may rupture into the air-passages. Rarely the hemorrhage is vicarious. Hemoptysis is occasionally observed in hysteria; Pende[1] has reported an instance of fatal hysteric hemoptysis in which no lesion could be found in the lung at autopsy. Pulmonary hemorrhage is sometimes observed in purpura, scurvy, and occasionally in leukemia. In pulmonary distomatosis[2]—endemic hemoptysis of China and Japan—hemorrhage constitutes a conspicuous symptom. Wright believes that in hemoptysis the inordinate hemorrhage often depends upon lessened coagulability of the blood. Reed[3] reports an instance of synchronous bilateral pulmonary hemorrhage brought about by a heavy lift. At the autopsy extensive interstitial hemorrhage was found in the central portion of both lungs; anatomically the lesion resembled an infarct. In a certain number of cases no assignable cause can be found; in a few of these the hemorrhage may recur a number of times without any discernible organic lesion preceding, accompanying, or following it. To this class properly belong vicarious hemoptysis, as well as that which may accompany pregnancy; in the latter instance cases are recorded in which successive pregnancies have been accompanied by recurring hemoptysis.

The effect of hemoptysis may be local or general. Locally, a slowly manifested hemorrhage may be aspirated into the air-vesicles and gradually inundate the bronchial system; a marked or severe hemorrhage may rapidly flood the respiratory passages and be immediately fatal. The hemorrhage can develop so slowly that no phenomenon during life is observed, and postmortem much of the lung may be found filled with the effused blood. If large cavities are present in the lung, hemorrhage may fill them with blood and cause death without blood-spitting. The general phenomena are those of shock. If death occur during the attack, the lung postmortem is more or less distended or inundated with blood; antemortem and postmortem coagula are found in cavities, when such are present, as well as in the bronchi. Patients rarely die as a result of the bleeding, consequently the causes may be of more interest than the hemorrhage.

Hemorrhagic infiltration, or **infarction**[4] (*pulmonary embolism*, or *pulmonary apoplexy*), consists in an arrest of the circulation in a given area of the lung, vascular rhexis with infiltration of the intervesicular structure, and effusion of blood into the air-vesicles.

The condition results from occlusion of a branch of the pulmonary artery by a thrombus (autochthonous embolism) or an embolus. The latter usually reaches the heart from the venous circulation, as in phlegmasia alba dolens, or arises in the heart, notably the right auricle. The processes of thrombosis and the origin of emboli have been con-

[1] "Morgagni," July 9, 1904. "Münch. med. Woch.," Oct. 25, 1904, p. 1938.
[2] See p. 192.
[3] "Western Med. Review," July 15, 1902, vol. vii, No. 7.
[4] Gebele, "Beitr. z. klin. Chir.," von Bruns, Tübingen, 1904, xliii, No. 2. Oppenheimer, "Berl. klin. Woch.," Feb. 3, 1902. Keyes, "N. Y. Med. Jour.," April 5, 1902. Miller, "Amer. Med.," Aug. 2, 1902. McPhedran and Mackenzie, "Trans. of the Assoc. of Amer. Physicians," 1903. Tiedemann, "Zeit. f. klin. Med.," Bd. 50. Hödlmoser, "Zeit. f. Heilk.," Bd. xxv, H. 5, p. 109. Hadeler, Inaug. Diss., München, 1904. Connell, Amer. Med. Assoc., Section in Surgery, June 10, 1904; also "Med. Record," July 2, 1904, p. 39. Robinson, "Med. Record," Jan. 14, 1905.

sidered. (See p. 278.) Where a thrombus forms, fibrinous plugs occlude the vascular supply to the affected part, and a cone-shaped area marks the outlines of the infarct. With clearly formed areas of hemorrhage, not to be differentiated from known areas of infarction, sometimes no embolus or thrombus, or source of either of these bodies, can be demonstrated. Feebleness of the circulation favors the occurrence of pulmonary infarcts and probably some are inflammatory.

Morbid Anatomy.—Postmortem, the changes found depend somewhat upon the extent of the area involved and upon the age of the infarct and its character.

When the lodged embolus is massive, occluding the pulmonary artery at its bifurcation, and when death occurred immediately upon its lodgment, the lung does not show the condition here considered as pulmonary apoplexy; it may manifest no conspicuous change. In typical cases of recent embolism the infarct appears, under the pleura, as a dark-red, almost black, mass, varying in diameter from one centimeter to five centimeters, rarely larger, and on section is found to be more or less wedge shaped, truly conic, with the apex of the cone directed toward the center of the lung. The color of the affected area varies from a gray, in extremely leukemic blood, to a black; as the process grows older the color passes from black to reddish-brown, and, with the gradual resorption of blood coloring-matter and resolution, the normal color may, in favorable cases, return. While the typical pulmonary infarct is conic or wedge shaped on section, the extensive anastomosis of the pulmonary circulation often affords so abundant a collateral blood supply that the area may be almost globular, or pear-shaped, and ovoid on section. The pleura over the area is at first normal, but soon shows a beginning exudate. Many post-operative pleurisies are of embolic origin. There is usually considerable edema surrounding the infarct. If the process is not infected—it is the noninfected variety which is now under consideration—and the area is small, absorption is possible. It is probable, however, that a certain amount of cicatricial tissue always develops, and, in not a few instances, a fibroid area remains.

Fig. 291.—Lung, Hemorrhagic Infarct. (Natural Size.) *A*. Pleura. *B*. Small infarct centrally placed. The large infarct shows the elevation of the pleura, the hemorrhagic suffusion of the central area, and the periphery of inflammatory hyperemia.

Histologically, the area consists of plugged vessels, with blood in-

filtrated into the septa and vesicles. In a short time after the infiltration the red corpuscles undergo hemolysis, disintegrate, and the resulting pigment diffuses into the adjacent tissue. The leukocytes increase in number, and, if the area involved be small, the products may pass off by the lymphatics, which, in many cases, become permanently pigmented by the process. If the area be larger and the tissue reaction greater, some fibrous tissue results; in more marked cases a puckered, pigmented, fibrous area forever marks the site of the lesion. If the bronchial artery, as well as the branches of the pulmonary artery, be occluded, the area may undergo a simple softening, fibroid change may occur around it, and lime salts may infiltrate it. The embolus causing the process may organize *in situ* and permanently occlude the vessels, or resolution may occur.

If the embolus contained bacteria, or should the area of the infarct become infected by organisms capable of inducing suppuration, an abscess results; if the saprophytic bacteria gain ingress and survive, gangrene may be engendered; if the embolus represented a part of a malignant tumor, a new focus of development is assured. Emboli containing the micro-organisms of the chronic infections lead to secondary nodules in the lung. The emboli associated with the latter processes—abscess, gangrene, neoplastic growth, and chronic infections—are so small that little hemorrhagic infiltration may accompany them.

Pulmonary atelectasis occurs in two forms—the congenital and the acquired.

Congenital atelectasis, or **apneumatosis,** is that condition of the lungs resulting from failure to expand following birth, the organ retaining its fetal characters.

The lungs may fail to expand as the result of inefficient respiratory effort or weakness. Extremely feeble infants may not be able to expand the whole lung. The condition may also result from plugging of a bronchus by aspirated solids, or even fluids, during delivery. If the infant survive for some weeks, the imperforate bronchi associated with the collapse will usually show dilatation in the affected area, the extent of the dilatation depending upon the duration of life and the amount of inspiratory force which the child has been able to exert.

Morbid Anatomy.—The condition may involve a part or the whole of one lung, or may be scattered as irregular foci in both lungs. The areas of atelectasis are usually most abundant and largest posteriorly in the lower lobes. When the collapse has been due to inefficient respiratory efforts, the introduction of air through a blowpipe, inserted into the bronchus, will usually lead to expansion. When the atelectasis is the result of mechanical obstruction by foreign bodies, the collapsed areas can not be fully expanded in the manner just described. The atelectatic portions are darker in color than the surrounding expanded lung, do not crepitate, and sink in water. When the areas are small and not abundant, the infant may recover; under such circumstances gradual distention may be brought about, or degenerative or proliferative changes may lead to connective-tissue substitution, followed by contraction, and, in time, but little evidence of the lesion may remain.

Acquired atelectasis, or **collapse,** is the condition observed when a part of the lung which has once expanded loses its air and does not refill

Pulmonary collapse results from the introduction of gas, fluids, or solids into the pleura, the first arising from puncture of the lung or chest-wall, or both; the second from pleuritic effusions, dropsical or inflammatory, or hemorrhage into the pleura; the third from tumors. Bronchial obstruction is a frequent cause; the occlusion may be due to a foreign body, a mass of false membrane, a clot of blood, or a plug of mucus; the bronchus may be collapsed by pressure from without, as when an enlarged peribronchial lymph-node, tumor, or aneurysm presses upon it. The influence of pressure may be shown in aortic aneurysm, pericardial distention, mediastinal tumors, spinal curvature, etc.; the pressure may be insufficient and the atelectasis partial at first, but if the cause continues to act, the collapse becomes complete. When due to bronchial obstruction, the condition is called *obturation atelectasis;* collapse resulting from external pressure is known as *compression atelectasis.*

Morbid Anatomy.—When the collapse affects the whole lung, as in pleurisy with effusion, the organ is pressed upward and toward the mediastinum and against the spine. The organ or the affected area is pink or pale gray in color, is firm and airless, is tough, tearing with difficulty, and often can not be distended; firm adhesions may bind it down, and the pleura may have become so thickened, fibroid, and resisting that reexpansion can never occur. When small areas of collapse occur, as in bronchopneumonia, in the recent state, they appear as small depressed spots, immediately under the pleura, bluish-purple or bluish-brown in color; occasionally lividity develops on exposure to the air; surrounding these areas the vesicles are distended (compensatory emphysema) and are pink or reddish-white, in contrast to the darker collapsed portions. If the collapse be recent and the occluded bronchus not too firmly obstructed, a blowpipe, or even firm pressure on the surrounding areas, may refill the collapsed vesicles. Later, from stasis in the vesicular wall, the color becomes much darker, and blood escapes into the connective tissue; the mass is soft and resembles the spleen in texture (**splenization**). Later, the blood to a certain extent is absorbed, the vesicular walls coalesce, proliferated connective-tissue cells and leukocytes form a young cellular tissue, and the mass is now in the condition called **carnification.** With the completion of contraction and organization a firm fibroid area results, known as the **cirrhosis of collapse**; these areas contain a relative excess of pigment, are pink at first, later gray, and are said to show **gray induration.**

Emphysema is a condition characterized by an excess of air in the lung. Two forms of the affection are recognized: in one the excess of air is in the connective tissue of the organ; in the other it is in the overdistended vesicles.

Interstitial emphysema, also called **interlobular emphysema,** is a condition in the lung comparable to subcutaneous or surgical emphysema involving the subcutaneous structures in fracture of the nose, or to the gas generated in the tissues in some forms of gangrene.

The condition usually results from ruptured air-vesicles, and occasionally occurs in violent coughing, as in whooping-cough, or bursting of distended air-sacs in vesicular emphysema. It is frequently due to pulmonary injury resulting from fractured ribs and penetrating wounds

of the chest. In the latter condition interstitial emphysema may occur without pneumothorax, provided air does not gain ingress through the thoracic wall. It has recently been shown that pneumothorax may result from infection of the pleura by the Bacillus aërogenes capsulatus of Welch. It is probable that in a similar manner an interstitial pulmonary emphysema might be induced.

Morbid Anatomy.—Interstitial emphysema may be readily detected postmortem by the large blebs found immediately under the pleura, differing from overdistended air-vesicles in that the former can be pushed around from place to place beneath the serosa. When the rupture occurs near the root of the lung, not only does the air reach the surface of the organ by the interlobular connective tissue, but it may find access to the mediastinal structures and the connective tissue of the neck.

Vesicular emphysema is a condition in which the alveoli and infundibular passages are dilated.

When the emphysema consists of overdistended vesicles in one area occupying the space and receiving the air that should be distributed in another part of the lung, the condition is spoken of as **local, vicarious,** or **compensatory emphysema.** As the condition may be acute,—*e. g.*, around an atelectatic area,—the withdrawal of the cause terminates the emphysema; when the cause persists, the acute dilatation becomes permanent; at first there may be no wasting, but eventually the intervesicular septa atrophy and this form passes into true emphysema.

Substantive, substantial, idiopathic, hypertrophic, or **large-lunged emphysema**[1] is a well-marked condition, readily recognized clinically, and possessing pathologic lesions eminently its own

Causes.—There seems to be necessary a hereditary tendency, a congenital deficiency in the lung tissue, in the absence of which emphysema is not likely to occur. Exactly what constitutes this hereditary deficiency has not been determined; the view that it is a defect in the elastic tissue is entirely consistent with the facts, but probably is not demonstrable. In two instances observed by Orth the appearances suggested a congenital hypoplasia, and he is of the opinion that some pulmonary injury or developmental defect modifying the elasticity of the organ is the essential factor in the production of emphysema. The disease is hereditary, in the sense indicated, and results from tissue peculiarity transmitted from the parent. Given the first element,—congenital weakness of the vesicular structures,—the second is heightened intravesicular tension. This may be brought about in two ways—(1) *inspiratory* and (2) *expiratory.*

1. *Inspiratory Distention.*—The vesicular distention of compensatory emphysema is, of course, inspiratory; and as true vesicular emphysema is almost always associated with catarrhal lesions, which favor atelectasis, the possibility of inspiratory distention acting as the cause can not be overlooked. The constant association of catarrhal inflammation

[1] Campbell, "West London Med. Jour.," July, 1897, p. 190. Collingwood, 'Med. Soc. of London," Jan. 12, 1903; also "Brit. Med. Jour.," Jan. 17, 1903, p. 139. Prettin and Leibkind, "Münch. med. Woch.," Feb. 9, 1904, p. 259. Conford, "Brit. Med. Jour.," June 25, 1904, p. 1485. Orth, "Berl. klin. Woch.," Jan. 2, 1905. Malibran, "La Presse Méd.," Sept. 3, 1904, p. 563.

and the plugging of bronchioles, attended by collapse in the lobules supplied, leads to compensatory dilatation of adjacent vesicles, and eventually to overdistention of these structures. The plug of mucus now shifts, and another series of vesicles are expanded beyond their normal limits. These processes, frequently repeated, so overdistend the elastic tissue of the vesicular wall that the normal retractile power is lost or modified, and the air-vesicles are thereby rendered incompetent fully to empty themselves. The foregoing views with regard to the inspiratory hypothesis have been modified, and in part supplanted by the theory to be next discussed.

2. *Expiratory distention* acts by increased pressure applied to the lung by the thoracic wall, and coincident abnormal resistance to free exit of the expired air brought about by narrowing of the laryngeal chink, glottis, epiglottidean lumen, etc. During the violent expiratory effort incident to severe coughing, the costal cartilages and sternum are pushed forward, the extreme normal obliquity of the ribs is altered, and the pulmonary space at the apex is increased, thus permitting distention of the lungs at the apex or upper lobes and the anterior margins, these points showing the most marked change.

The causes active in increasing the expiratory stress are: (1) Coughs, as in chronic bronchitis, the violent respiratory strain of pertussis, etc. The fact that whooping-cough increases the vesicular tension is shown by the occurrence of interstitial emphysema induced by the violent respiratory effort. (2) Increased pulmonary tension induced by playing wind-instruments, heavy lifting, etc. The studies of Prettin and Leibkind of the thoracic condition in glass-blowers, and Fischer's examination of musicians, have cast discredit upon the previously accepted belief that such vocations are important factors in the production of emphysema. Collingwood's conclusions are that in the protected parts of the lungs the condition is induced by causes that are operative during inspiration, and in the unprotected areas—particularly the anterior margins and apex—the emphysema results from the heightened tension of exaggerated expiratory effort.

Morbid Anatomy.—In typical cases the chest is barrel-shaped, the most conspicuous alteration being an increase in the anteroposterior diameter. The sternum is pushed forward and the normal obliquity of the ribs greatly lessened. The heart is lower than normal, and the diaphragm depressed, resulting in abdominal displacement of the subdiaphragmatic viscera, particularly the liver and spleen. The costal cartilages are unusually rigid and frequently calcified; when the sternum is raised, the lung does not show the normal tendency to collapse—indeed, it may not retract at all, and may bulge forward. The anterior margin of the lungs extends over the pericardium to a varying degree when removed, they do not collapse; the pleura over the affected area is pale, anemic, dry, and the unaffected areas are congested; white patches occur on the pleura—the *pulmonary albinism* of Virchow. The emphysematous lines may follow the intercostal spaces, but the disease is most marked along the anterior margins, at the apex, and, less commonly, around the margin at the base. Large bullæ may be seen under the pleura, varying in size up to 0.5 or 1 cm., and at the free margin they may attain a diameter of 2 cm. or more. Where the emphy sema is most marked, the lung fails to crepitate. The absence of elas-

ticity is indicated by the fact that pits are obtained almost as readily as in edema, although edema is usually absent. In uncomplicated cases the weight is notably less than normal. The color depends upon the amount of pigment. Usually, the organs are pale and any residual pigment is conspicuous. As a rule, the pulmonary parenchyma contains less blood than normal; and even when death has been delayed, marked congestion and conspicuous edema are frequently absent. The lung, when handled, feels like a pillow stuffed with down (Laennec). The smaller bronchi may be dilated; more or less bronchitis and peribronchial induration are always present. The longitudinal bands of elastic tissue may be traceable in the bronchial wall. (See Fig. 293, p. 592.)

Morbid Histology.—If the lung be blown up and dried, the enormous size of the distended vesicles are rendered apparent; even on section in the recent state, the atrophic remains of the vesicular walls may be discernible with a hand lens. Hardened and examined, the elastic tissue is altered in quantity and quality, and the vesicular septa atrophied, permitting coalescence of adjoining cells; in the process of atrophy the capillaries disappear, and this, with the loss in septa, diminishes the aerating capacity of the lung. The most conspicuous changes will be observed in the elastica. In the largest blebs a few granules of this substance are scattered through the wasted walls; in other areas the elastic fibers are coarse, fragmented, swollen, and frequently show none of the undulations present in normal elastic tissue.

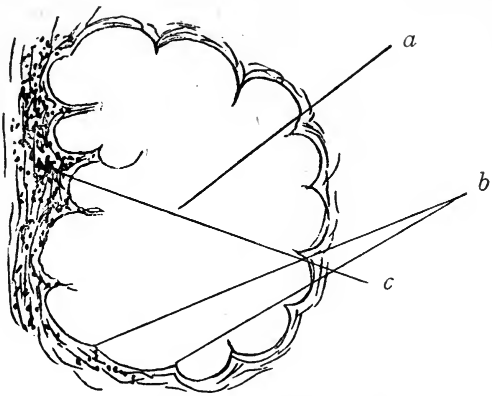


FIG. 292.—PULMONARY EMPHYSEMA.—(*Fütterer.*)
a. Emphysematous enlargement of an infundibulum. *b.* Atrophied intervesicular septa, improperly called absorbed alveolar walls. *c.* Pigment in the fibrous septum.

Changes in Other Organs.—The increased work demanded of the right heart in emphysema leads to hypertrophy and dilatation, the former in rare cases affecting the entire heart; sclerotic changes in the pulmonary artery with or without dilatation may occur. Other organs—particularly the liver, spleen, and kidney—subject to the alterations of structure incident to venous distention usually manifest that change.

Atrophic or **senile emphysema** (*senile atrophy of the lung, small-lunged emphysema* of Jenner) is, as its name indicates, a disease of advanced life, and is essentially an atrophic lesion of a lung in which very little, if any, distending force has been exerted. The chest is small, the ribs are oblique, thus decreasing the diameters and diminishing the capacity of the chest; the respiratory muscles are atrophied and the lung is smaller than normal; the changes in the vesicles and septa already noted in substantive emphysema occur. The enlargement in the size of the vesicles is attributed to atrophy of the intervesicular walls. The bronchi frequently show some dilatation; large bullæ are

usually absent; the lung commonly collapses on opening the chest, and, in contrast with large-lunged emphysema, not infrequently shows areas of congestion, edema, and infarction. There may be some doubt as to the propriety of classifying this condition with emphysema. The fact that custom has established the precedent does not, of course, prove its correctness. A better knowledge of atrophy, occurring in the lung, would probably lead to the recognition in this form of emphysema of some atrophic manifestation analogous to that seen in other tissues in advanced life.

Acute vesicular emphysema is observed in acute bronchitis and after death from asphyxia; there is also reason to believe that vesicular distention is present during life in these cases. That the condition is unassociated with atrophy of the vesicular walls is admitted. In the absence of such atrophy it consists largely of functional overdistention, and is not properly a disease of the air-vesicles.

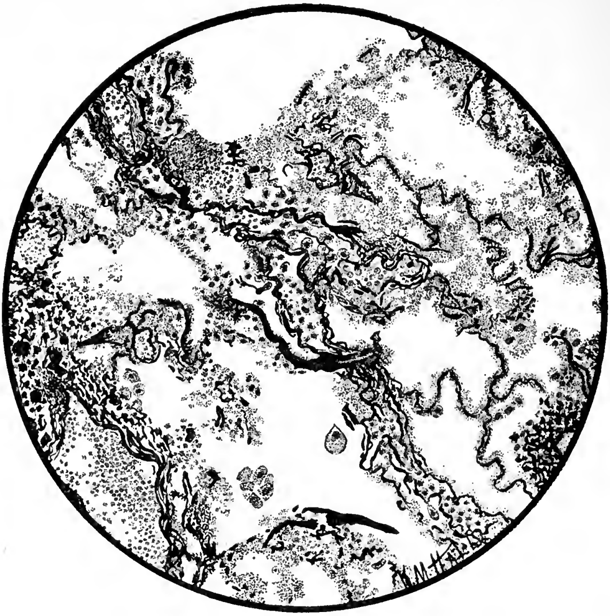


FIG. 203.—LUNG, EMPHYSEMA.
Weigert's elastica stain. Fragmentation and swelling of the elastica.

Pulmonary Suppuration,[1] Including Abscess of the Lung.—This condition is commonly described under the head of purulent pneumonia, suppuration pneumonia, etc., names indicating that it is some special type of pulmonary disease rather than the usual form of suppurative lesion. Etiologically and pathologically, and to a certain extent clinically, suppurative processes occurring in the lung possess no important difference from suppurations arising from pyogenic infection in other organs.

[1] Eisendrath, "Phila. Med. Jour.," Nov. 9, 1901. Bentz, "La Presse Méd.," 1902, No. 97. Jurewitsch, "Münch. med. Woch.," March 15, 1904, p. 480.

Primary pulmonary suppuration is an exceedingly rare condition, pyogenic infection may be brought to the lung in one of four ways. (*A*) *By the air-passages;* (*B*) *from contiguous structures;* (*C*) *by the blood;* (*D*) *by the lymphatics.*

(*A*) *By the Air-passages* (*Bronchogenic Suppuration*).—Although we are constantly inhaling large numbers of bacteria, many of them undoubtedly pyogenic, and in other ways pathogenic, the bactericidal action of the extruded epithelium, leukocytes, mucus, serum, etc., prevents ingress or pathogenic activity except the tissues be weakened by (1) *general debility*, (2) *previous local disease*, or (3) *accompanying injury*. As examples of these may be mentioned: of the first, the probability that fibrinous pneumonia in drunkards will present a mixed infection; of the second, pyogenic infection of tuberculous areas, or of the areas involved in lobar or lobular pneumonia, or in pneumoconiosis. In lobar pneumonia abscess formation is rare; the so-called purulent infiltration is not really pus, as it not uncommonly contains no pneumococci, and rarely, if ever, are the bacteria of suppuration present. If abscess formation takes place in pneumonia, it usually begins as scattered foci of infection, and, as such, is found postmortem; rarely, however, these foci extend and run together, the infection lessening or obliterating the circulation in the area, and more or less of a lobe may be converted into an abscess. Abscess formation in acute lobular pneumonia is still rarer.

Suppuration from injury with infection. Exploratory puncture of the pleura has caused pulmonary abscess. But the form of suppuration due to an injury which brings infection with the trauma, and both through the air-passages, is typified in the so-called aspiration pneumonia. Foreign bodies in the air-passages; suppurative processes in or around the larynx, trachea, or larger bronchi; deglutition pneumonia, in which, from altered innervation, food particles gain ingress to the air-passages; and allied processes, all may give rise to abscess formation by depositing an irritant, no matter how small, and with it the bacteria of suppuration. Bronchogenic pyogenous infection induces suppurative inflammation of the bronchi which extends into the contiguous vesicles and interstitial tissue. Polymorphonuclear leukocytes accumulate in large numbers, necrosis of the involved pulmonary structures occurs, and an abscess results. Commonly such suppurative processes are primarily restricted to lobules; frequently they are multiple, and coalescing with contiguous areas, may give rise to abscesses of considerable size.

(*B*) *Pulmonary suppuration* arising through extension of the infection *from contiguous structures* is not common, in the sense that the abscess extends by necrosis of the lung tissue; but in the lymphatics such extension may occur. Localized or circumscribed empyema, or pleural abscess, particularly when situated between the lobes or at the base, between the diaphragm and lung, may penetrate the pulmonary tissue by a gradually extending necrosis, and eventually may find evacuation through a bronchus. Abscess of the liver or suppurating echinococcus may perforate the diaphragm and infect the lung; Bentz records an instance in which a tuberculous abscess of the right iliac fossa communicated with a bronchus. Mediastinal abscess and other forms of peripulmonic suppuration may likewise induce suppurative

pulmonic lesions. Cancer of the esophagus may lead to direct infection of the lung tissue or of the air-passages.

(*C*) *Pulmonary suppuration from infection through the blood* (*hematogenous infection*) was the common sequence of preantiseptic surgery and obstetrics. Emboli containing the cocci of suppuration lodge in the lung and give rise to centers of infection, followed by abscess formation. These abscesses are small, usually multiple, superficially located, not uncommonly cone-shaped, with the base of the cone toward the pleura, into which they not infrequently rupture, giving rise to suppurative pleurisy (empyema or pyothorax), or, if communication has been established between the abscess cavity and a bronchus, thereby admitting air to the pleural cavity, there quickly results a pyopneumothorax. (See Metastatic Abscesses, p. 284.)

(*D*) *Infection of the Pulmonary Structure through the Lymph-channels* (*Lymphogenic Infection*).—An interstitial, peribronchial, or interlobular suppurative process may result from invasion of the lung tissue by way of the peribronchial lymphatics. Thus, in suppurative inflammation of the pleura (empyema) the lymphatics passing through the lung may be distended by infective material, or exudates eminently adapted to infection, and cocci accompanying the process or gaining ingress to the resulting lesion, may give rise to pus formation in the interstices of the lung; as the infection is in the lymphatics around the bronchi, it is spoken of as **peribronchial suppurative lymphangitis.** The condition can not be diagnosticated during life, and is recognized only postmortem. Pyogenic agents reaching the lung or its lymphatic system from the mediastinum or elsewhere may give rise to the process.

Morbid Anatomy of Pulmonary Abscess.—When solitary, the abscess may attain the size of a lobe; when multiple, they are usually small. The contents, in addition to pus, contains epithelial debris and remnants of lung tissue, the demonstration of which in the sputum is a valuable aid to diagnosis. If evacuation has occurred during life, the walls may be gangrenous and the cavity exceedingly fetid; if the mass be small and the patient in good condition, a fibroid protecting wall may form; ordinarily, however, the wall is formed, from within outward, by a layer of (1) necrotic disintegrating lung and inflammatory tissue; (2) a layer of solidified lung infiltrated with leukocytes and young connective-tissue cells, and commonly containing hemorrhages in the alveoli and interstitial tissue; (3) edematous lung tissue. If the pleura has not been opened, the abscess wall, formed by that structure, is covered by an abundant exudate of fibrin, and some cloudy serum, varying in quantity, will probably occupy the cavity. Purulent pleurisy (empyema) may occur without rupture of the abscess, but invariably results if rupture takes place, and is usually accompanied by pneumothorax, the latter depending upon whether the abscess communicates with an open bronchus. Rarely, a pulmonary abscess may encapsulate, as previously indicated; in lobar pneumonia, when the evacuation is complete, cicatrization has been known to occur; the same change has been observed in hepatic abscess discharging through the lung. The majority of cases terminate fatally. Sometimes infection is widespread and is not associated with distinct abscess formation. Under these circumstances the condition is one of peribronchial suppurative lymphangitis, mentioned above.

Attempts have been made to classify pulmonary abscesses according to the cause, as, pyogenic, tuberculous, actinomycotic, pneumonic, etc. But these processes, when terminating in pus formation, are essentially mixed infections in the vast majority of cases, and the primary disease does not materially alter the true character of the developed malady.

Gangrene of the lung[1] consists of two factors: (1) Death of a part of the pulmonary tissue (necrosis) or a material lessening of its blood supply and (2) infection, which must, in all probability, be polymicrobic. Infection alone often fails to produce this form of necrosis; obliteration of the blood supply does not insure gangrene; the lung tissue must be killed, or its resistance to bacteria greatly reduced, and coincident, or subsequent, infection then completes the process. If pyogenic infection occur in a lung the blood supply of which is abundant, suppuration is induced, pus being a product of vital reaction to pyogenic mycotic invasion; if, however, the tissue be dead, if vital processes be materially weakened, the tissue resistance reduced, the nutrition greatly modified by existing lesions, or, it may be, arrested, the pyococci and associated organisms give rise to gangrene.

The causes of pulmonary gangrene, then, embrace all those conditions that materially lessen or arrest nutrition and permit infection—lobar pneumonia, aspiration pneumonia, foreign bodies in the bronchi, pulmonary embolism, bronchiectasis, suppurative conditions in the lung, pressure, as from tumors and aneurysms on the bronchi and blood-vessels, etc. The cases of pulmonary gangrene that accompany, or, more commonly, follow, severe febrile processes are probably infections in areas of hypostatic or hemorrhagic pneumonia. Brain abscess and middle-ear and mastoid disease, by infectious thrombosis of the sinuses, frequently induce pulmonary embolism, which, being infected, is often followed by gangrene or abscess. The same is true of infectious processes in the venous system elsewhere. The bacteriology of pulmonary gangrene has been studied by a number of observers; the results have been collated by Ophüls, who adds five personal observations. In many of the cases acid-fast bacilli and organisms resembling the streptothrix group are present. The germs possessing the characters of tubercle bacilli may mislead the uninitiated, but are usually easily recognized by experienced observers. Rosenberger[2] has shown that within certain limits it is possible to differentiate a number of these organisms. Anaerobic bacteria are usually present.

Morbid Anatomy.—Two forms are recognized: the *diffuse or disseminated* and the *circumscribed*. The division made, independent of any surgical conception of the affection, seems well adapted to the modern surgical divisions of gangrene—circumscribed and spreading. Clinicians recognize a **latent pulmonary gangrene** characterized by the absence of the usual symptoms, notably the offensive odor of the breath and the fetid expectoration. In some of the latent cases the area involved is large and may be multiple.

[1] Withington, "Boston Med. and Surg. Jour.," March 10, 1898. Ophüls, "Jour. of Med. Research," June, 1902, vol. viii, p. 242. Hölzle, Inaug. Diss., Munich, No. 136, 1903. Steven, "Lancet," Oct. 15, 1904, p. 1077. Büdinger, "Münch. med. Woch.," Oct. 18, 1904, p. 1874. Anders and McFarland, "Medicine," Feb., 1902.

[2] Publications from the Laboratories of the Jefferson Medical College Hospital, 1904, vol. i.

Diffuse pulmonary gangrene, like the spreading form of the surgical affection, is rare, and commonly follows pneumonia, and, although less frequently, obstruction of the pulmonary artery. There is not a sharp line of demarcation between the healthy and diseased tissue; a whole lobe, or the greater part of a lobe, is involved, the process being well marked at the center of the diseased area, but gradually fading into the surrounding zone of highly inflamed pulmonary tissue.

In the **circumscribed pulmonary gangrene** there is a sharp line of demarcation between the dead and the inflamed tissue, and, although the foci may be multiple, each area involved is clearly outlined in the living pulmonary structure.

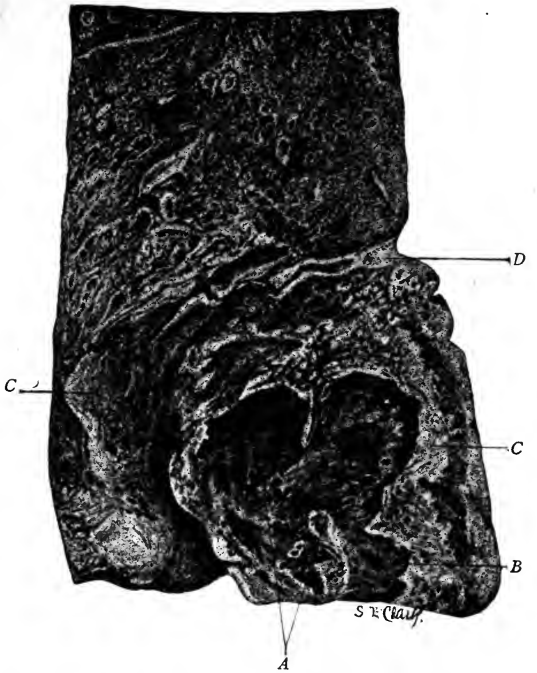


FIG. 294.—PART OF RIGHT LUNG, CIRCUMSCRIBED GANGRENE. *A*. Two pockets of gangrenous cavity. *B*. Dilated bronchus with gangrenous walls. *C*, *C*. Solidified zone of pulmonary inflammation. *D*. Adhesion between superior and inferior lobes. *E*. Beginning abscess at margin of gangrenous area.

The gangrenous mass in either case is, as a rule, extremely fetid, and during life this foul penetrating odor is imparted to the breath, and persists for hours in the sputum. The latter, when left in a conic glass, usually manifests a tendency to separate into three layers: the uppermost is thick, frothy, yellow or green or greenish-yellow in color; the middle stratum is a clear serous fluid, but slightly tinted; the sediment is greenish-brown, occasionally pus-like, and contains the characteristic odor in its fullest concentration. Elastic fibers are not always present, although they usually are to be found; Eijkman[1] has shown that certain bacteria evolve an elastica-dissolving enzyme, and it is possible that the disappearance of elastic tissue in pulmonary gangrene may be attributable to the action of some such substance. The color of the diseased tissue is dependent upon the stage and, probably to a large extent, upon the character of the infection. Early, it is brown or reddish brown; and later, quite black. The color-changes are in part brought about by the presence of blood pigment, to which the brownish hue is to be attributed. The blackening is partly due to changes in the hemal iron as well as to the presence of iron-free pigment. The occasional greenish hue, which may be marked, is

[1] "Centralbl. f. Bakt.," Nov. 5, 1903, p. 1.

due to changes in normal pigments or to the presence of the bacillus pyocyaneus. In the earlier stages the gangrenous tissue may retain its structure, but disintegration rapidly ensues, and a cavity with ragged irregular walls forms, inclosing a green or reddish-yellow mass of softened necrotic tissue. Passing into, often across, the cavity are remains of blood-vessels and bronchi. By reason of the infectious character of the lesion, the blood-vessels are not occluded, as normally, by an organizing thrombus; the coagulum forming in the lumen being infected, is easily displaced, permitting hemorrhage, which may be recurrent, and in rare cases fatal. Around the gangrenous area there is a zone of deeply congested or intensely hyperemic tissue, which is usually solidified, and outside of this an area of marked edema with leukocytic infiltration. Cicatrization and recovery may occur; the disease is more commonly fatal.

Pneumonia.

The term pneumonia is used to embrace all the inflammatory lesions of the pulmonary tissue, often including some of the processes already considered; for example, pulmonary suppuration is sometimes spoken of as *septic pneumonia* or *suppuration pneumonia*. When the term pneumonia is used alone, without any qualifying phrase, croupous pneumonia is usually meant. The forms of pneumonia commonly considered are *lobar* or *croupous pneumonia*, *catarrhal pneumonia*, or *bronchopneumonia*, *interstitial* or *fibroid pneumonia*, and, by some writers, the desquamative pneumonia of tuberculosis.

Lobar, Croupous, or Fibrinous Pneumonia[1] (*Pneumonitis; Lung Fever*).—The fact that the pleura is usually involved has led to the name *pleuropneumonia*. This disease is an acute inflammatory affection of the lung due to infection.

[1] Norris, "Amer. Jour. of Med. Sci.," June, 1901. Blumer, "Albany Med. Annals," Aug., 1901. Fisher, "Amer. Jour. of Med. Sci.," Aug., 1901. Foulerton, "Lancet," Aug. 17, 1901. Busquet, "Revue de Méd.," Feb. 10, 1902. Burt, "Amer. Med.," April 26, 1902. Littlejohn, "Edinburgh Med. Jour.," April, 1902. Maschke, "Cleveland Med. Jour.," May, 1902. Sears and Larrabee, "Med. and Surg. Reports of Boston City Hosp.," twelfth series, Dec. 1, 1901; also "St. Paul Med. Jour.," July, 1902. Hare and Dare, "Med. News," Aug. 23 and 30, 1902. Hans Kohn, "Berl. klin. Woch.," Nov., 1903. Spitta, "Brit. Med. Jour.," Nov. 15, 1902, p. 1579. Washbourn, Croonian Lectures for 1902; "Lancet," 1902, vol. ii. Wadsworth, "Amer. Jour. of Med. Sci.," May, 1904. Ebstein, "Münch. med. Woch.," May 5, 1903, p. 761. Rosenow, "Jour. of Infectious Diseases," March 19, 1904, p. 280; also "Jour. Amer. Med. Assoc.," March 18, 1905. Kerr, "Trans. of Chicago Path. Soc.," May 11 and June 8, 1903. Tchistovitch, "Annals de l'Inst. Pasteur," May 25, 1904. Goss, "Arch. des Sc. Biol. de St. Petersburg," 1904, No. 5, p. 429. Durck, "Münch. med. Woch.," June 28, 1904, p. 1137. Callender, "Brit. Med. Jour.," July 16, 1904, p. 116. Koawa, "Berl. klin. Woch.," 1904, No. 14. Stuertz, "Zeit. f. klin. Med.," 1904, Bd. lii, p. 422. Rau, "Zeit. f. Heilkunde," 1904, H. 1. Tarchetti and Curlo, "Gazz. degli Osped. e delle Clin.," 1904, March 27, p. 387. Manges, "Med. Record," Dec. 10, 1904, p. 929. Wells, "Jour. Amer. Med. Assoc.," Sept. 24, 1904. Morse, "Amer. Med.," Jan. 28, 1905, p. 153. Heyman, "Thèse de Wurtsbourg," 1904. Bottomley, "Brit. Med. Jour.," Feb. 4, 1905, p. 237. Wollstein, "Jour. of Exper. Med.," 1905, vol. vi, Nos. 4, 5, and 6, p. 391. Ramsdell, "Amer. Med.," Feb. 11, 1905, p. 237. Kieffer, "Amer. Med.," March 4, 1905, p. 356. Pratt, Contributions to the Science of Medicine by the Pupils of William H. Welch, 1900, pp. 265 to 277.

That pneumonia is a disease due to bacterial invasion is now universally admitted. That it is, however, the result of a single organism seems no longer probable, although not absolutely disproved. The germ most frequently present is the Diplococcus pneumoniæ,[1] which was described by Sternberg as the micrococcus of rabbit septicemia, and named by him the micrococcus of Pasteur. This organism was later studied by a number of observers, and was found by Fränkel and Talamon in the lung in croupous pneumonia; it is sometimes called the pneumococcus of Fränkel.

In 1882 Friedländer described an organism[2] associated with pneumonia, to which he gave the name pneumococcus. As a result of later studies the germ is now held to be a bacillus. Croupous pneumonia clinically and anatomically not to be differentiated from croupous pneumonia produced by the pneumococcus of Fränkel may result from infection by streptococci, and possibly staphylococci, although it is usually held that the presence of the latter organism is to be attributed to a mixed or secondary infection, and that, even when found alone, the primary pneumonia was due to the pneumococcus or other bacterium which has disappeared. The Bacillus typhosus, Bacillus influenzæ, colon bacillus, plague bacillus, and possibly a number of micro-organisms may bring about that form of solidification usually regarded anatomically characteristic of croupous pneumonia. The pneumococcus is present in from seventy-five per cent. to eighty per cent. of the cases examined postmortem. The anatomic distribution of the lesion would indicate that infection usually takes place through the bronchi. Atypical distribution, and occasionally associated lesions, would lead us to admit the possibility of primary hematogenous infection.

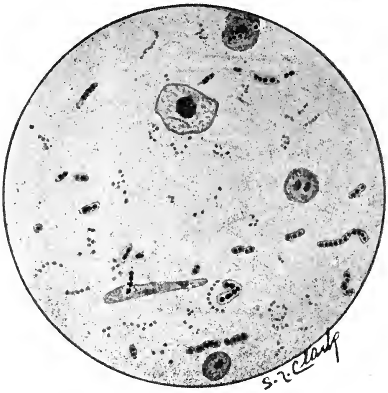


FIG. 295.—SPUTUM, CROUPOUS PNEUMONIA.
In the extreme upper part of field is a leukocyte showing chromatolysis but containing englobulated cocci. Below and slightly to the left of this cell is a squamous cell from the mouth. To the right of the latter and slightly below is a polymorphonuclear leukocyte, and in the extreme lower part of the field is a small hyaline cell. The field also contains numerous encapsulated pneumococci, a few streptococci, and unarranged cocci that can not be accurately identified.

Certain *predisposing causes* are recognized. These act in one of two ways: (1) By altering the saliva, and thereby the culture medium in which the organism is growing; these changes in the pabulum increase the virulence of the pneumococcus; (2) the predisposing elements so weaken the tissues that infection becomes possible. The latter is illustrated by the frequency with which pneumonia occurs in drunkards, in the debilitated, in Bright's disease, and after contusions of the chest. Of the two hypotheses it seems the more reasonable, and but little importance is usually attached to the first given.

All ages are liable, but pneumonia is most frequent in three periods —early childhood, between twenty and forty, and after sixty. It is

[1] For description see p. 109.
[2] For description see p. 127.

more common among males than females; where both are subject to the same influences, there is little difference. Of Sears and Larrabee's 949 cases, 714 were males. Conditions disturbing the equilibrium of the pulmonary circulation, as chronic heart disease, retention of excrementitious matters, as in uremia,—in other words, any process reducing the vital powers and enabling infection to occur,—favor the development of pneumonia. Unhygienic environment acts in two ways —(*a*) by reducing resistance and (*b*) by favoring the accumulation of infectious material in the surroundings. The specific cause elucidates the occasional occurrence of epidemics in crowded or unhygienic quarters. That unsanitary environment is not necessary to the production of an epidemic is shown by records of hospitals and institutions where children are housed in large numbers. In the epidemic of pulmonary inflammations observed by Spaet 13.9 per cent. of the population suffered. It has been shown experimentally that exposure to cold and dampness increases the susceptibility of animals. There seems to be an individual predisposition, as manifested by the frequent recurrence of pneumonia in the same individual, twenty-eight attacks having been observed in one patient (Loomis). That relapses do not commonly occur seems to indicate a condition of acquired immunity; that such is of brief duration is also presumable from the susceptibility to recurrent attacks. Experimentally, it has been shown, in animals, that a certain degree of immunity may be secured by the injection of filtered bouillon cultures of the pneumococcus or a glycerin extract prepared from the growing organism. The immunity is temporary, lasting but a few months, but during that time is transmitted, in gestation and by nursing, to the offspring. The serum of such animals has been used with beneficial results in the treatment of pneumonia.

Morbid Anatomy.—Pneumonia involves, as a rule, either a whole lobe or a whole lung, most commonly the lower right lobe; the lower left lobe is next in order; third in point of frequency is double pneumonia, while pure croupous pneumonia of the apices is rare. The right apex is more frequently involved than the left. Kerr's statistics show that the affection is unilobar in forty-two per cent. and unilateral in eighty-four per cent. of the cases. The lesion is double in from twelve to fifteen per cent. of the cases. The whole of the affected lobe or lung is usually in the same stage, although wandering, creeping, or **migratory pneumonia,** involving one lobe after another, shows different stages in different lobes; in such cases the lower lobe is most frequently first involved. In rare instances one lobe and part of another may be affected, and in different stages. Occasionally, central changes precede peripheral lesions, and the center of the lung is gray, while the periphery is less advanced—**central pneumonia**; rarely, the reverse may be demonstrated. In double pneumonia one lung may be further advanced than the opposite organ. In infancy and in old age the apex is more frequently the initial point of invasion; in the aged, death occurs earlier in the attack than in middle life. When the disease is one-sided, the unaffected lung is commonly deeply hyperemic and congested.

For purposes of description it is customary to recognize three stages, called (1) engorgement, (2) red hepatization, (3) gray hepatization. Pratt's studies show that the differences between the red and the gray

hepatization can not be detected histologically; in other words, that the color upon which the differentiation rests is not characterized by a constant histologic picture.

State of Engorgement.—When the chest is opened, the lung does not retract or collapse with its wonted rapidity; there may be a slight shrinking in volume, but the general contour of the organ is likely to be retained. The lung, or the area involved, is red, often a scarlet hue. Crepitation is present throughout, but is less distinct than normal; the specific gravity is greater than in health, as is shown by the fact that while the lung floats, it does not float as high as the normal organ. Occasionally, the pleura shows evidence of beginning inflammation. (See p. 476.) On section, the color is uniform; as a rule, blood oozes from the cut surface, and while in the majority of the cases the blood is thick, flowing slowly, in some cases an abundant transudate of serum appears immediately on section, which, mixing with the blood, bathes the incised surface, and drips, or even runs, from the dependent edge. On microscopic examination the capillaries of the vesicular walls are found enormously distended, tortuous, and even saccular; the epithelium of the vesicles is swollen and, in places, desquamating; in the few vesicles with marked desquamation some leukocytes and red blood-corpuscles may be demonstrated. The subpleural and interlobular connective tissue also shows the engorgement, and the lobules may be outlined under the pleura by the intensely distended vessels.

This stage lasts from a few hours to two or three days; rarely the latter. It seems reasonable to suppose that in the last moments of life, or even after death, solidification may occur, or, having already developed, may extend. Thus, the author has made postmortems after the most experienced clinicians had, but a few moments before death, outlined the area that seemed solid; in not a few of these cases has the solidification been found far beyond the outlines indicated by the physical examination made just before death. This offers some consolation for undiagnosticated areas of solidification, but it is also explained by assuming that, after death, the lung rises, as a result of retraction or partial atelectasis of the unsolidified areas above. Death rarely occurs in this stage except when great exposure, an alcoholic debauch, or other debilitating antecedent conditions are incident to the attack.

The stage of engorgement is often found in one part of the lung when another area is more advanced, or in one lung when its fellow is solidified. It seems reasonable to assume that, in very rare cases, recovery may occur without further progress of the morbid process.

Stage of Red Hepatization.—The stage of engorgement terminates by the distended blood-vessels pouring out an inflammatory exudate into the air-vesicles, and thus, by excluding the air, bringing about the stage of solidification. The lung, or affected area, on opening the chest, shows absolutely no tendency to retract; it is voluminous, and may be marked by the ribs; the color is darker than in the first stage, or rather more of a brown or reddish-brown; the area involved is solid, and the absence of air is shown in the entire freedom from crepitation, in the absolute dullness, great weight, and, when thrown into water, the rapidity with which the part involved sinks. On section (see

Lung. Croupous Pneumonia. Stage of red hepatization.

(Fox's Atlas.)

Plate VII), the organ is dry, rough, and granular; a finger passed over the scraped surface gives to the observer the impression of a rough surface, not unlike ground glass; this and the granular appearance are due to the plugs of fibrin that occlude the vesicles and on section project; they may be scraped out or picked out with a needle, and often an infundibulum with attached cast of the vesicles, or a bronchial plug, may be removed. The area is friable, and gives way when the finger is thrust into it; a thick slice cut from the surface breaks when bent; there is nothing more characteristic than this fact. The weight of the normal lung rarely reaches 400 grams; the lung in croupous pneumonia may weigh three or six times as much.

Morbid Histology.—On microscopic examination the blood-vessels are less distended than in the preceding stage, although they are still fuller than normal. The inflammatory exudate poured out from the vessels now occupies the vesicular cavity. When the exudate passed from the vessel it was liquid (liquor sanguinis), but in the vesicle coagulation of the fibrin has solidified the intravesicular contents and entangled the cellular elements present. With the transudation of the liquor sanguinis leukocytes (by diapedesis) and erythrocytes (by rhexis) escape into the vesicular cavity. Thus there are found in the vesicle leukocytes, red corpuscles, and a few desquamated epithelial cells entangled in a meshwork of fibrin fibrillæ. In some cases the fibrin is more abundant at the periphery of the vesicles; commonly, however, it is fairly uniformly distributed within the affected alveoli. I have seen the lines of fibrin parallel, but usually an interlaced or web-like fibrin mesh is present. Often threads of fibrin pass through the vesicular wall. The smaller and sometimes relatively large bronchi contain fibrinous plugs. The character and number of the leukocytes are not always the same in different cases, nor are the same cells present in all the alveoli of the affected area. Undoubtedly the virulence of the infecting organism exerts different chemiotactic powers upon the individual leukocytes of the blood; in some cases the mononuclears are the first to appear and are the most conspicuous cells; this is in accord with Pratt's observation. Polymorphonuclear leukocytes often appear early and persist with decreasing numbers into the later stages. The small amount of epithelium contrasts strongly with the abundance

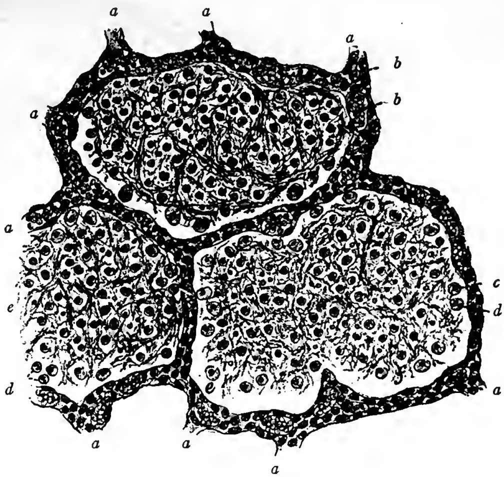


FIG. 296.—THREE ALVEOLI FILLED WITH FIBRINOUS EXUDATE. CROUPOUS PNEUMONIA, STAGE OF HEPATIZATION.—(*Schmaus.*) 250 diameters.

a, a, a, a, a, a, a, a, a. Alveolar septa with somewhat distended capillaries, as at *b, b.* *e.* Meshwork of fibrin occupying the cavity of the air-vesicle. Two other air-vesicles, also filled, are shown. In this solidified exudate are entangled desquamated epithelial cells, *c,* from the alveolar wall and leukocytes, *d, d.*

of that element in the air-vesicles in bronchopneumonia. The demonstration of the presence of fibrin is best accomplished by Weigert's method. (See p. 252.)

The solid exudate extends into the bronchiole, and may, in rare instances, reach bronchi of considerable size. The connective tissue of the lung is the seat of more or less swelling, rarely marked, and the lymph-spaces, particularly near the hilum of the organ, are often distended by leukocytes. The accumulation of leukocytes around the

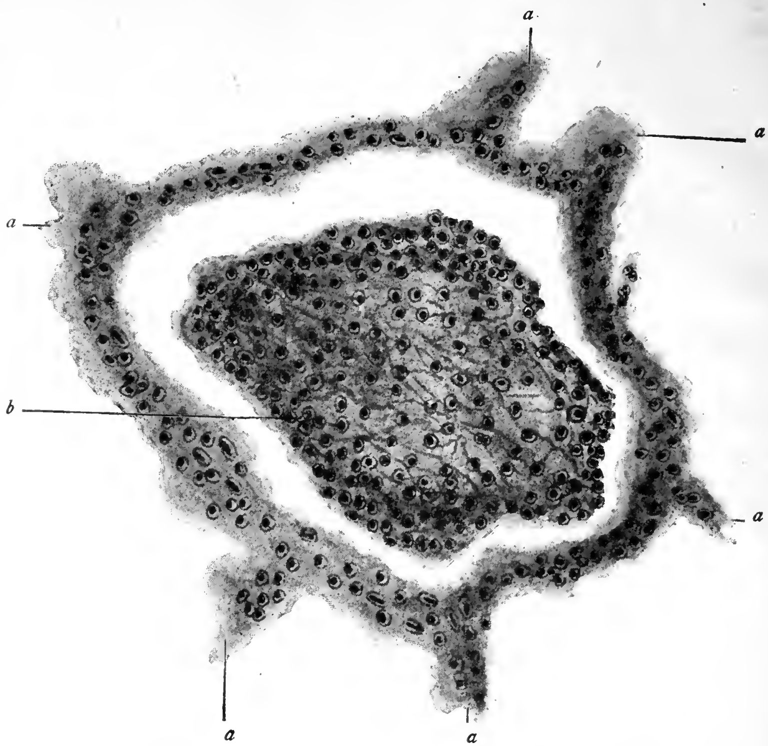


Fig. 297.—Croupous Pneumonia. Single Air-vesicle in the Second Stage, with Slightly Contracted Exudate. (1/8-inch objective, 1-inch ocular.) Much higher magnification than in figure 296, with the object of bringing out the fibrinous network.

Specimen fixed in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin, and mounted in balsam. *a, a, a, a, a, a.* Vesicular walls. *b.* Exudate in the air-vesicles; during life the unoccupied area around the exudate either contained serum or the contraction may have occurred during fixation and hardening.

bronchi is less evident than in catarrhal pneumonia. Suitably prepared sections usually show abundant pneumococci, and the occasional presence of other organisms, to which reference has been made.

If evidence of pleurisy did not develop in the earlier stages, it is certain to do so now. A thin plastic layer or a marked fibrinous exudate may be present. When a past pleurisy has obliterated the sac by universal adhesion, an exudate is often present in the newly formed connective tissue; when the synechia is old and cicatrization firm, it

is less susceptible to inflammatory infiltration. Serous exudates are rare, and, from the very nature of the lung lesion, can not be large.

Whether or not a desquamative process preceded the stage of exudation at present under consideration there is now induced desquamation of the epithelial lining of the vesicles. The fibrin contracts, and free fluid collects in the vesicle or is taken up by the lymphatics. The red blood-cells undergo fragmentation and disintegrate, and bronchial inflammation with some of the features of a bronchopneumonia occurs. The presence of desquamated and fatty epithelium is associated with liquefaction of the coagulum in the vesicle and conversion of the mass into an emulsion favorable for absorption or expectoration. These changes usually alter the color of the organ from red to gray, and the condition is spoken of as gray hepatization. The duration of the stage of red hepatization no doubt varies; in three days after the onset of symptoms the lung may be gray; on the other hand, the author has examined a lung thirty-nine days after the initial chill, and thirty-seven days after the clinical diagnosis of solidification, and found the organ still red.

Gray Hepatization.—When this stage is reached, the lung no longer resembles, in its gross appearance, the previous stage, just described. As indicated, the organ is reddish-gray, gray, or yellowish-gray, depending upon the degree to which the stage is developed; the affected tissue is much softer and less tense than in the red stage, tearing with the greatest ease, but is less readily broken by bending. The incised surface is moist and smooth, in contrast to the dry and rough surface observed in the red stage. (See Plate VIII.) In gray hepatization squeezing the organ leads to a rather free flow of the partly emulsified inflammatory exudate.

The peribronchial lymph nodes are enlarged, the pleurisy is more advanced, and occasionally the lymphatic channels, running from the pleura toward the mediastinum, are swollen and show as light yellow or yellowish-red streaks. The involved area is still airless, at least in the earlier stages of the gray change, as may be shown by the tests already given when considering the airless condition of the organ in red hepatization. Under the microscope, in the later stage of gray hepatization, no fibrin can be demonstrated, but the vesicles are filled with cellular elements resembling those of bronchopneumonia; there are more leukocytes and desquamated epithelial cells in varying stages of granular and fatty change, and there is less serum than in the bronchopneumonic exudate. The coagulability of the fluids that bathe the cut surface in the gray hepatization can be shown by thrusting the organ into strong alcohol, aqueous solutions of picric or chromic acid, or boiling water, thereby coagulating the albuminous constituents of the vesicular contents. The firmness and resisting density of the red stage can not, however, be redeveloped, as the material which solidifies at this stage is albumin undergoing coagulation, and not fibrin.

Terminations.[1]—It is reasonable to suppose that the gray stage is the beginning process of resolution. As a result of autolytic and fatty changes, the softened vesicular exudate eventually becomes transformed into an emulsion that is absorbable and sufficiently liquid to permit

[1] For the formation of abscess in lobar pneumonia see p. 594. Gangrene resulting from lobar pneumonia is also there described.

extrusion from the air-vesicles and expectoration. The quantity leaving the lung by absorption may be in excess of that escaping by the bronchi, or the reverse. The amount of the exudate (estimated by weighing the normal lung and deducting its weight from that of the inflamed organ) varies for the entire lung between 1 kilogram and 1800 grams; by observing how little may be expectorated, the capacity of the absorbents can be, in part, appreciated. It is probable that this absorbed material is largely cared for by the lymphatics, as such exudates are not likely to pass through even capillary walls. The termination of lobar pneumonia in interstitial pneumonia will be considered with the latter. Occasionally, croupous pneumonia apparently terminates in tuberculosis. In such cases the tubercle bacillus may have

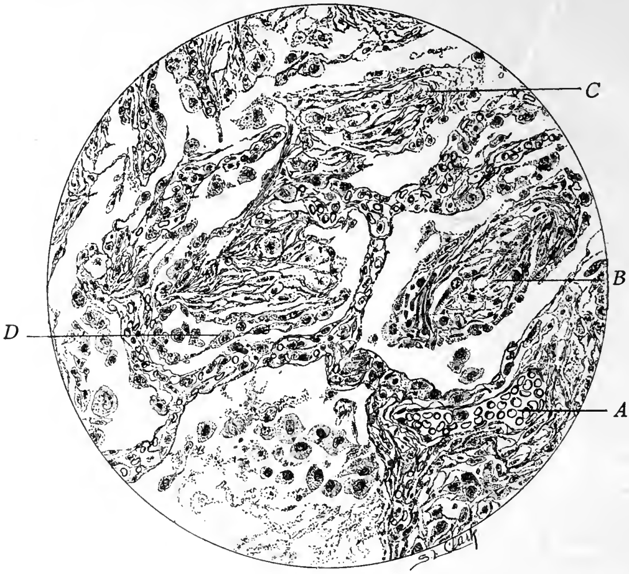
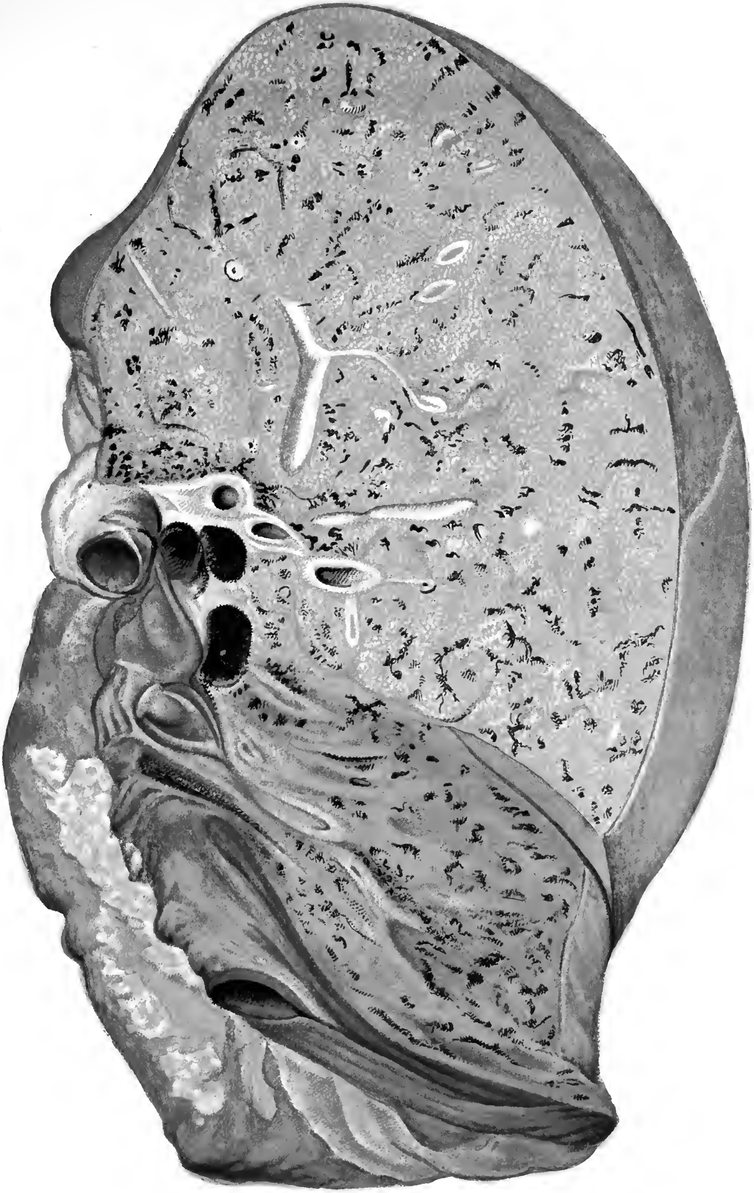


FIG. 298.—LUNG, CROUPOUS PNEUMONIA, ORGANIZATION OF THE INTRAVESICULAR EXUDATE.
The duration of the pneumonia in the case from which this specimen was obtained could not be determined with accuracy. The clinical data indicated that the organ had certainly been solid over six weeks. *A*. Vessel in intervesicular septum. *B*. Slightly granular partly organized intravesicular plug. *C*. Point of attachment of organizing exudate to inner wall of air-vesicle. *D*. Proliferating vesicular epithelium. In the vesicle below that into which the leader from *D* runs are many large cells apparently epithelial in origin, lying free in the cavity with a small amount of granular detritus.

been in the lung in some quiescent nodule, or the lesion may be the result of a secondary infection in the tissues weakened by the pneumonic process.

Unresolved, organized, or **organizing pneumonia** results when resolution is long delayed and active infection suppressed. The condition is also called **chronic pneumonia.**[1] The essential phenomenon of the process is the gradual substitution of the fibrinous contents of the air-vesicles by fibrous tissue developed from the intervesicular structures. In the earlier stages continued proliferation and desquamation

[1] See "Nothnagel's Encyclopedia of Medicine," American edition, volume on "Diseases of the Bronchi, Pleura, and Lungs," 1903, p. 685.



Lung. Croupous Pneumonia. Stage of gray hepatization. The pleura on the right and at the base shows the fibrinous exudate, modified from Bollinger.

of the epithelium can sometimes be recognized. Outgrowths from the connective tissue of the intervesicular wall gradually extend into the cavities of the air-cells, which are eventually filled by a hyaline, rather imperfectly developed fibrous tissue. The vessels supplying the new structure are derived from the pre-existing capillaries of the alveolar wall. Before the completion of the process the newly formed tissue is attached by a pedicle to the wall of the air-vesicle at the point from which it arose. Eventually the pulmonary tissue contracts and the affected structures become paler and firmer. Any residual epithelial cells disappear, the newly formed intra-alveolar fibrous tissue merges with the vesicular wall, and obliteration of the pulmonary parenchyma is completed.

Lesions That May Accompany Croupous Pneumonia.—*Pleurisy* is always present in a pneumonia that reaches the surface of the lung. Pleurisy of the base with pneumonia of the apex, and inflammation of the opposite pleura, are combinations of pathologic interest. While the pleurisy is usually manifested by a slight plastic or an abundant solid exudate and little serum, it is not invariably so; abundant serous exudates occasionally occur, and empyema (suppurative pleurisy) is not so infrequent as was once believed. It is now established that the pneumococcus is the essential etiologic factor in various forms of pleurisy, and that it may, without mixed infection, induce suppuration.

Pericardial inflammation accompanying pneumonia partakes of the same general character already described as present in pleurisy, and is due to the same cause. It occurs most commonly in pneumonia of the left lung, and especially when that part of the lung overlying the pericardium is the seat of the disease.

The *blood changes* that occur in croupous pneumonia, although not characteristic, are important. There is a notable increase in the number of polymorphonuclear leukocytes; poikilocytosis is occasionally present; the alkalinity of the blood is decreased. Although not of unvarying import, increase in the leukocytes is considered a favorable prognostic omen. Tchistovitch believes he has demonstrated that the crisis results from the accumulation of phagocytes in the pulmonary tissue. It is well known that leukopenia is often marked in fatal cases. During the active stages of the disease the pneumococcus is frequently present in the blood; Rosenow found it in ninety-one per cent. of 175 cases studied.

The *heart muscle* may show cloudy swelling; less commonly, advanced granular change; and, rarely, a well-marked fatty degeneration, or a frank acute nonsuppurative myocarditis may be in progress. Myocardial infective processes have not been observed. Cardiac thrombi on the left side develop rarely, except immediately preceding death, and when associated with endocardial inflammation. Just preceding death, in the agonal period, the slowed and greatly obstructed circulation of the right side may be embarrassed by clots extending from the right ventricle into the smaller ramifications of the pulmonary artery, and, at the postmortem, these may be pulled out as long tree-like or whip-like masses.

Endocarditis, both acute simple and acute malignant, occurs. The acute simple form has been found without the observer being able to demonstrate pneumococci in the blood or cardiac lesion; they are,

however, commonly present. In the malignant form of endocarditis accompanying pneumonia the pneumococcus is invariably present, and in a small percentage of the cases other organisms of suppuration occur in the vegetations and blood.

Monarticular joint inflammations have been frequently noted, and are extremely likely to terminate in suppuration. It is interesting to note that pneumococci have been found in the affected joints, in the pus from the joints, and that arthritis has been induced by the intra-articular injection of the organism

The extreme selection of serous surfaces by this organism and its products is further illustrated in the occasional *peritonitis* and inflammation of tendon sheaths that have been observed.

Meningitis is another illustration of the liability of serous surfaces to suffer; while it may occur with malignant endocarditis and be accompanied by embolic processes, both may be absent. All the intracranial serous structures may be the seat of the disease, or it may be restricted to a single fossa or region or to the base. Infection occurs through the blood or from the nasal or aural spaces, and the seat of the lesion may indicate the source of the infection. The process may be restricted to the meninges or the brain structure may be involved. Involvement of the spinal meninges has been observed.

A number of mucous membranes may be infected by the pneumococcus, either during pneumonia or independently; the most frequent are the ear (*otitis media*) and mucous surfaces of the nasal appendages; *e. g.*, *abscess of the frontal sinus*, containing the diplococcus and followed by a diplococcus-meningitis. Anders reports three cases of cholecystitis complicating croupous pneumonia. *Suppurative parotitis* (the pus containing the diplococci) is occasionally observed. Fibrinous inflammations of the stomach, colon, and other mucous surfaces may occur; hemorrhagic and gangrenous processes are less frequent, except in the embolic phenomena which accompany malignant endocarditis. The epithelium of the mucosæ, liver, and kidneys is usually cloudy. The renal lesion in croupous pneumonia, manifested by the presence of more or less albumin in the urine, rarely passes on to an inflammatory condition which persists after the disappearance of the initial cause. In fatal cases an *acute diffuse* or *acute nonsuppurative interstitial nephritis* is often observed. *Thrombosis* of one or more veins and *thromboarteritis* sometimes occur. Either of these may give rise to gangrene. An instance of *acute thyroiditis*, the pus of which contains pneumococci, is recorded. Among the complications involving the nervous system may be mentioned *acute cerebritis*, *monoplegias*, *hemiplegias*, and *neuritis*.

Bronchopneumonia[1].—This disease is also known as **lobular pneumonia,** a name objectionable in that it does not indicate the bronchial

[1] Steven, "Lancet," Sept. 20, 1902, p. 791. Richat and Goepfert, "Rev. mens. des Mal. de l'Enfance," Aug., 1902. Joachmann and Moltrecht, "Zentralbl. f. Bakt.," 1903, xxxiv, 15. Robertson, "Scottish Med. and Surg. Jour.," June, 1903, p. 485. Conner, "N. Y. Med. Jour.," Dec. 26, 1903, p. 1213. Laignel-Lavastine and Voisin, "Arch. Gen. de Méd. et path. Anat.," March, 1904, p. 206. Bovaird, "Med. News," April 30, 1904, p. 820. Hardy, "Lancet," Sept. 24, 1904, p. 885. Woolstein, "Jour. of Exper. Med.," 1905, vol. vi, p. 391. Sutherland, "Harveran Soc. of London," Feb. 9, 1904; also "Lancet," Feb. 25, 1905, p. 502.

association that is always present, and also in the fact that embolic processes may be essentially lobular and still bear no relation in point of cause or pathology to the condition under consideration. The name **catarrhal pneumonia** indicates the character of the exudate, but not all its component parts are catarrhal in point of origin, and the changes to be noted in the vesicular wall make the process more than a superficial inflammation. The designation **capillary bronchitis** is objectionable, as it does not indicate the accompanying vesicular change. The term *disseminated pneumonia* indicates the wide distribution of the process in contradistinction to the more or less circumscribed lesion of croupous pneumonia. The term *catarrhal bronchopneumonia* seems no better than bronchopneumonia alone. The various other synonyms that have been given in attempts to indicate the location or character of the lesion, the cause or termination, are either obsolete or objectionable.

Causes.—Bronchopneumonia is not, as a rule, a primary disease, but arises secondarily in some other process. Conner has collated the experiences of a large number of observers and concludes that probably less than thirty per cent. to thirty-five per cent. of the cases are primary. In nearly all, if not all, the cases of this disease the bronchiole or the passage above is the initial seat of the lesion, and the vesicle is secondarily affected. When the inflammatory process follows disease of the intervesicular wall, such as tuberculosis of that structure, one can conceive the initial lesion to have been in the vesicle; but, aside from this factor,—contiguous disease,—bronchopneumonia, as the name indicates, begins essentially as a bronchial inflammation.

While no specific germ has been adduced, the phenomena are those commonly attributed to infection or infectious products. The pneumococcus of Fränkel is present in a relatively large percentage of the cases; it may occur alone or be associated with other organisms. Meuniér has shown that the only organism present may be the Bacillus influenzæ; streptococci and other pyococci are sometimes found. The condition is so constantly a part of various infections that it would seem that the definite anatomic alterations to be described might arise from a multitude of causes, a few acting singly, or the combination of two or more factors. The fact that bronchopneumonia occurs most constantly, as an important process, in the young and the aged seems to indicate some peculiarity of tissue at those periods; this has been assumed to be, in part at least, an inability of the terminal air-passages to evacuate themselves, owing to the faulty or poorly developed elastic tissue in the lung of the young, or muscular weakness of the respiratory apparatus in the two extremes of life; further, the epithelium of the infant, in the transitional stages of development, is most abundantly exfoliated as a result of an irritation that adult tissues would resist. That such excessive susceptibility of the mucous surfaces exists is shown in the gastro-intestinal diseases of childhood equally as much as in the pulmonary lesions. Bovaird states that in the Foundling Hospital forty per cent. of the dead have bronchopneumonia. A similar susceptibility is manifest in old age.

Unsanitary surroundings, crowding, poorly ventilated sleeping or living rooms, are all predisposing elements. Exposure, cold, dampness, and other incidents of the winter months show a marked influence,

the disease being most prevalent from November to May, inclusive, reaching its acme in the uncertain, varying, climatic conditions of the early spring months. Its relation to the infections is shown in the constancy with which it develops in the presence of those conditions; of the acute infectious diseases, measles is the one with which it is most frequently associated, although diphtheria, both pharyngeal and laryngeal, especially the latter, is commonly the immediate precursor or accompanying lesion. Scarlet fever and whooping-cough are usually, and typhoid fever and smallpox may be, accompanied by bronchopneumonia.

When the respiratory apparatus is the seat of any of the specific infectious diseases, whether acute or chronic,—anthrax (as in woolsorter's disease), tuberculosis, glanders, leprosy, etc.,—bronchopneumonia is extremely liable to occur; and when one of these processes involves the lung, catarrhal pneumonia is inevitable. The bacillus of tuberculosis in the lung, whether in the cavities of the alveoli, as when aspirated from above, or in the vesicular or bronchiole wall, as when brought by the blood or lymphatics, always incites a bronchopneumonia, which is modified by the tuberculous process, but is, nevertheless, a characteristic lesion. Bronchopneumonia may be present in syphilis of the lung.

When infectious materials are drawn into the lung, as in the deglutition and aspiration pneumonias, to which reference has already been made, bronchopneumonia and other accompanying infective processes ensue; that bronchopneumonia is not the whole of the process is shown by the frequency with which suppuration or gangrene may follow. (See Pulmonary Suppuration, p. 592.) Bronchopneumonia also terminates fibrinous or lobar pneumonia when resolution is gradually reestablishing the normal.

In conclusion, it remains to be said that any condition that lowers the vitality of the individual, that weakens the avenues open for infection, that depresses or debilitates, favors the development of bronchopneumonia. To this group of causes belong Bright's disease, chronic heart disease, convalescence from acute processes, or the debilitating influences of more chronic ones. Bronchopneumonia to a varying degree always accompanies pneumoconiosis

Morbid Anatomy.—In recent cases, acute in time, the lung is more voluminous than normal, and does not collapse with usual promptness, and may not shrink in the least when the chest is opened; there is not that dense firmness of the tissue involved so constantly present in fibrinous or lobar pneumonia. and on superficial examination the lung appears to crepitate throughout; examined more closely, areas that do not crepitate are easily found; while firm, they are not dense, and are small nodules in contrast to the large areas of fibrinous pneumonia. On the surface of the lung, as a rule, near the base are areas sunken below the surface, blue or bluish-brown in color, usually isolated and small, although in rare instances almost, if not quite, all of a lobe may be involved in the atelectatic process. Usually, such areas can be reexpanded by forcing air into the bronchus. The area joining that of collapse is not uncommonly emphysematous, as are the anterior and apical margins. At scattered points will be found projecting areas, over which the pleura may be rough or even show a beginning exudate;

the larger the consolidated portion, the more evident the pleurisy. On section, the surface is usually dark or reddish, although in adults it may be gray at points—not unlike the gray stage of fibrinous pneumonia. The surface is smooth and moist, and drips blood or bloody serum. The outline of the affected lobules can be seen, or, where a number have run together, they usually manifest different stages of the process, and can in that way be distinguished. A suitable lobule, on longitudinal section, shows the grape-like structure of the lung, with alveoli, infundibula, and bronchiole filled with puriform mucus; a transverse section reveals the central bronchiole, containing a tenacious plug of mucus, surrounded by distended vesicles and the adjacent collapsed lobules. Adjoining the inflamed tissue the areas of

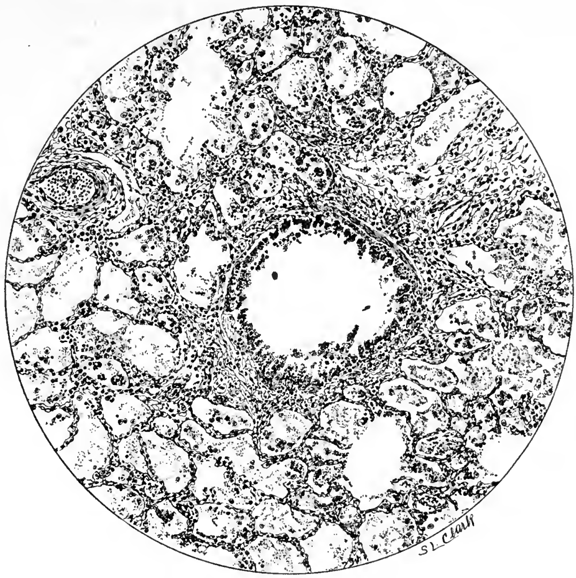


Fig. 299.—Lung, Including a Small Bronchus. Bronchitis and Bronchopneumonia.
The bronchus (center of field) shows desquamation of epithelium, many of the cells being completely detached and others in process of detachment. The bronchial wall is infiltrated by mononuclear leukocytes. Many of the adjacent air-vesicles contain a granular deposit resulting from precipitation, during fixation, of an albuminous exudate; in this granular materia are varying numbers of mononuclear cells and epithelial cells the latter having been cast off the alveolar walls.

collapse may be readily distinguished, or they may be indistinct; if defined, they are dark, smooth, airless, and instead of bulging when cut, apparently retract; when immediately subpleural, there may be ecchymosis in or over them; when not well defined, the outline is formed by darkish bands traversing the lobes in an irregular manner. The peribronchial lymphatic nodes are usually swollen and edematous, owing to the effort made to care for the degenerative product of the bronchial and vesicular inflammation. In some cases the lymphatics traversing the lung are also distended.

Morbid Histology.—If a drop of the fluid that fills the air-spaces be squeezed out upon a slide, it will be found composed of germinal, granular, and fatty epithelium, a varying number of leukocytes,

rarely any red blood-cells. The fluid exudate must be solidified before making sections for histologic examination; this may be accomplished by thrusting a part of the affected tissue into boiling water, and thus coagulating the albumin in the serum and incarcerating the cellular elements; such a process alters the surrounding structures too profoundly to be commendable, and the same object may be secured by using absolute alcohol or Flemming's or Hermann's fixing solutions. (See p. 33.) Infiltration is imperative in order to retain the histologic structure in place.

Examination of properly prepared sections discloses the alveoli filled, not with a fibrin-bearing exudate, as in lobar pneumonia, except in a very few scattered vesicles, but with a mucoid exudate containing the cellular elements previously indicated, the epithelium being especially conspicuous. The bronchiole lumen will be found occluded by the same exudate, the wall infiltrated by leukocytes, and the integral elements pushed apart, typifying the swelling that was present. Longitudinal sections reveal, in the bronchiole, more or less irregularity in the transverse diameter—saccular dilatation. The infundibulum and its surrounding vesicles are filled with a similar exudate, and the same cellular infiltration of the vesicular walls may be found. Toward the margin of the affected lobule the distention is less marked, and the alveolar epithelium shows desquamation and marked fatty changes. The capillaries of the walls, both vesicular and bronchial, are usually distended and surrounded by leukocytes. The lymphatic channels leading from the affected areas are usually engorged. In the peribronchial lymphatics more or less swelling and infiltration are manifest.

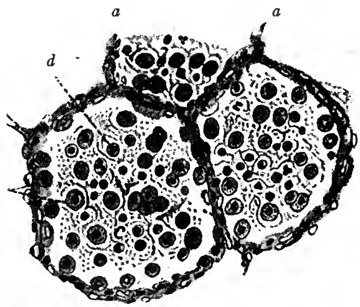


FIG. 300.—TWO ALVEOLI AND A PART OF A THIRD FROM LUNG IN CATARRHAL PNEUMONIA.

a, a, a. Walls of the alveoli. *b.* Desquamated epithelial cells from the walls of the alveolus. *c.* Alveolus filled with catarrhal exudate. *d.* Leukocyte.

In the bronchopneumonia accompanying the aspiration of foreign bodies into the bronchi the bacteria present infiltrate the connective tissue, abundant leukocytic infiltration occurs, and, if the processes have sufficient time, suppuration or gangrene usually ensues.

Terminations.—Acute bronchopneumonia undergoes resolution rapidly once the process begins; upon withdrawal of the cause the lymphatics and blood-vessels dispose of the unexpectorated exudate, epithelium rehabilitates the denuded walls, and resorption of cellular products in the vesicular and bronchiole tissues follows the removal of the liquid exudates that caused the swelling to which reference was made while considering the histology. The feebleness of the respiration and the reduced resistance may enable deposited bacteria to secure a more or less permanent abode. That pyogenic and saprophytic bacteria may induce suppuration and gangrene has already been stated. In the distended vesicles or lobules tubercle bacilli may lodge, and the characteristic phenomena of tuberculosis ensue, constituting a tuberculous infection secondary to the bronchopneumonia. This, while pos-

sible, is no doubt rare, and where caseation with fibroid encapsulation of the caseous area is found postmortem, it is probable that the disease was tuberculous from the start, but that the conservative elements limited the process; these areas may become calcareous, and exhibit the other phenomena so constantly associated with quiescent tuberculosis. It is possible for tuberculosis to follow a more wide-spread infiltration, or the tubercle bacillus may have induced the pneumonia. At one time it was believed that caseation and fibroid change were legitimate terminations of bronchopneumonia, and recognized as frequently occurring conditions. While, as already stated, one can conceive of a simple nontuberculous area of consolidation becoming fibroid and limited, independent of the bacillus of tuberculosis, still, when caseation and calcareous infiltration are found, the evidence is clearly that of a "healed-in" tuberculous focus.

The complications of bronchopneumonia are fewer and occur less frequently than those observed in croupous pneumonia. The catarrhal lesions of the upper air-passages are not properly considered as complications. *Empyema* is probably the most important coincident affection or sequel. *Meningitis* is occasionally observed; Hardy encountered it eight times in 150 cases; he places it among the causes of bronchopneumonia. *Joint complications* are infrequent, but Bichat and Goepfert have shown that they may occur and be due to the pneumococcus or other pyogenic organisms. *Endocardial* and *myocardial* changes of importance are usually the result of the condition which caused pneumonia, and not truly a consequence of the latter; to this statement there are occasional exceptions. In some cases a *leukocytosis* occurs. Simple uncomplicated attacks are rarely attended by changes in the kidneys or important structural alterations in the liver.

Fibroid pneumonia,[1] **interstitial pneumonia, chronic interstitial pneumonia,** *pulmonary cirrhosis*, or, more properly, *pulmonary sclerosis, fibroid induration, fibroid lung*, with various other synonyms, is a chronic productive inflammatory process, involving essentially the connective tissue of the organ, with increase of the fibrous elements and more or less contraction of the newly formed structures. The degree to which the change may progress is dependent upon many factors. The fact that the process, practically always, is secondary to some other lesion, has led to a multitude of names, each assuming the existence of a separate condition. No inflammation of the lung tissue, no invasion of the pulmonary structure by foreign bodies, whether coal or iron, bacteria or morbid growths, is likely to occur without a certain amount of increase in the fibrous tissue. This statement indicates the character of the causes which are active. Fibrinous pneumonia, bronchopneumonia, tuberculous pneumonia, and other infectious processes which may induce inflammation,—as syphilis, leprosy, and actinomycosis, pneumoconiosis, and inflammation of the pleura,—may all be cited as etiologic factors.

When the cause is limited to a part of the lung, the fibroid change may involve only a small area; thus, a small circumscribed, possibly

[1] See Vogel, "Ziegler's Beitr.," 1900, vol. xxviii. Auld, "Brit. Med. Jour.," Feb. 4, 1905, p. 236. Also article on "Chronic Pneumonia," "Nothnagel's Encyclopedia of Practical Medicine," American edition, volume on "Diseases of the Bronchi, Pleura, and Lungs," 1903, p. 685.

quiescent tuberculous process in an apex may be surrounded by an insignificant area of advanced interstitial fibroid change. When a protracted bronchopneumonia has involved, for any great length of time, the entire pulmonary structure, increase of fibrous tissue will be present throughout both lungs, the bronchial walls will be thickened, and many intervesicular septa more or less fibroid. Attempts have been made to classify these various stages and degrees, but one lung may be in one stage and the other contain similar lesions developed to quite a different degree; one lung may be universally fibroid, the other show only points of fibroid change—the so-called local fibroid pneumonia. As to source or cause, the fibrous-tissue increase follows out certain lines.

In fibrinous pneumonia the area involved may not undergo resolution, but pass into this condition of fibroid change. The connective-tissue cells in the vesicular wall proliferate, and the fibrinous plugs occupying the vesicles and infundibula pass through the various stages of embryonic and granulation tissues, and eventually the mass becomes converted, more or less completely, into fibrous tissue—a condition spoken of as the *gray induration of unresolved pneumonia.* The area is gray, firm, elastic, and smooth, and closely resembles recently developed but slightly contracted connective tissue. The process is one of the infrequent terminations of croupous pneumonia. In persistent bronchopneumonia the inflammatory changes, already noted as occurring in the vesicular wall, lead to thickening, and in the areas of collapse this may preclude restoration of function. The most marked development of fibrous tissue occurs around the bronchi,—a peribronchitis,—followed by the fibrous invasion extending to the septa between lobules, and eventually to the vesicular walls.

When fibroid lung follows an inflammation of the pleura,—**pleurogenous interstitial pneumonia,**—the condition is usually associated with plastic pleurisy, the formative inflammatory process extending into the lung along the course of the interlobular septa and peribronchial lymphatics. This differs etiologically from the fibroid condition already described as occurring in the more or less completely collapsed lung with thickening of the pleura and constriction of the lung by an interstitial process; the shrinking or contraction of the organ is secondary to the development of new fibrous tissue; in the collapsed lung the fibroid change is secondary to the pleural thickening and the cessation of function.

The development of fibroid lung in pneumoconiosis has already been considered;[1] it remains only to be said that the increase in fibrous tissue there noted is due to the direct influence of the foreign bodies in the connective tissue of the lung, exactly as fibrous tissue develops around any extraneous body in the process of "healing-in"; to this must be added the thickening incident to the accompanying inflammation of the mucous surface, such as always occurs when persistent inflammation leads to fibrous changes in the submucosa. (See Fig. 269, p. 544.)

Morbid Anatomy.—From the foregoing it will be seen how varied the appearance of such organs must be. In the simpler, less extensive,

[1] See Pneumoconiosis, and other infiltrations of mucous membranes, p. 542; also Chronic Catarrhal Inflammation of Mucous Membranes, p. 546.

and generally disseminated lesion the organ is firmer than normal, and on the pleura the fibroid areas between lobes or lobules may be recognized. On section, these areas of fibrosis appear as gray, more or less pigmented masses, usually radiating from the central bronchus along the lines of the interlobar or interlobular septa. The uninvolved portions of the lung may be slightly emphysematous, and the elasticity of the organ so modified that it collapses slowly, if at all. In more advanced cases, or when the lesion is more marked, the fibrous tissue involves a whole lobe, or a greater part of a lobe, and is conspicuous; on section, it differs in degree only from the next condition to be described, in which the whole of a lung is usually involved.

This constitutes *true cirrhosis*, or, better, *sclerosis of the lung*. Of necessity, the process is unilateral, and the corresponding chest-wall shrunken and pulled in, and the shoulder lower than that of the unaffected side. The opposite lung is voluminous, extends far beyond the median line, is emphysematous, and the mediastinal tissues, heart, and great vessels are displaced toward the affected side. The diminished volume of the fibroid lung may be incredible; the author saw a case in which it was not larger than two small fists, and Osler speaks of an instance in

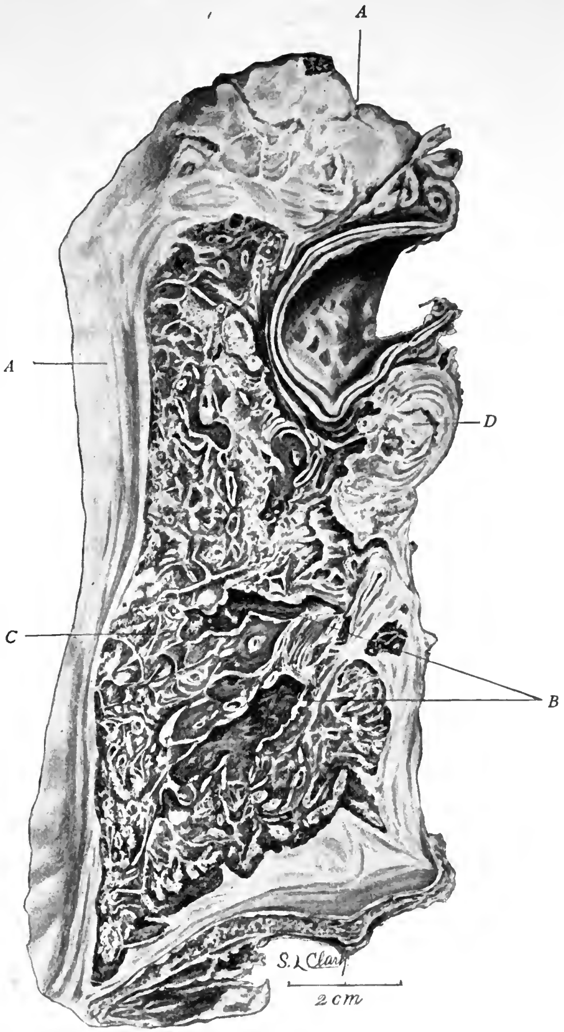


FIG. 301.—LUNG. CHRONIC INTERSTITIAL PNEUMONIA, BRONCHIECTASIS, HYALOSEROSITIS, AND A TERMINAL CATARRHAL PNEUMONIA RESULTING FROM CONCURRENT INFECTION BY THE TUBERCLE BACILLUS AND PNEUMOCOCCUS.

A, *A*. Greatly thickened pleura. *B*. Dilated bronchi. *C*. One of many broad strata of fibrous tissue irregularly traversing the organ. *D*. Large caseous lymph-node near hilum of lung, and immediately adjacent to the aorta, a section of which is shown just above. The aorta is the seat of slight atheroma.

which the affected organ was not found (!). The lung is firm, at times doughy and airless, and resists the knife to an unusual degree. In the pleurogenous form, and when the process follows croupous pneumonia, the pleura may be adherent, and is always very much thickened; when the condition results from intrapulmonary causes, the pleura may not be affected. The bronchi are nearly always more or less dilated, sometimes to an enormous degree. (See Bronchiectasis, p. 579.) The cut surface shows the fibroid character to advantage; the blood-vessels and bronchi are embedded in a mass of grayish, rather dense, often hyaline, and sometimes partly calcified, fibrous tissue. The slowness of the circulation and the loss of functional activity in the affected organ render infection readily possible; rarely, this may be pyogenic, and leave a cavity. Tuberculosis as a cause and tuberculosis as a sequence —an infection of a point of least resistance, as this truly is—occurs in no small number of cases; the relation of the tuberculous process to the interstitial change can usually be inferred by the location and character of the lesion. The cases of tuberculous origin frequently show an apical cavity and some evidence of infection in the opposite lung.

Morbid Histology.—This has been partly considered in the preceding remarks and varies as does the gross anatomy. In the less marked cases fibrous tissue in varying stages of development may be found in the vesicular walls and around the bronchi; in the advanced cases—those last considered—the bands of fibrous tissue have compressed and obliterated the pulmonary vesicles, and converted the areas involved into irregularly outlined masses of cicatricial tissue. A varying amount of catarrhal inflammation may be evident in the vesicular structure or the change indicative of a past catarrhal process may remain. Evidence of tuberculosis can often be demonstrated microscopically when the grosser lesions are lacking.

Termination.—Under the most favorable circumstances, in nontuberculous cases, arrest of the process is all that can be expected. This is dependent upon the possible removal of the cause. In a vast majority of cases tuberculosis is the last and fatal stage; Auld reports an instance in which tuberculosis, beginning in an unresolved pneumonia, became arrested. The limited fibroid change—local interstitial pneumonia—around a point of tuberculous infection may be beneficent in that it is possible by this means to limit the dissemination of a localized tuberculosis, and the increase of connective tissue with calcareous infiltration, as so often occurs, is no doubt the local reaction to an infection by which contiguous and general extension is prevented.

Pulmonary tuberculosis,[1] tuberculosis of the lung, and tuberculous

[1] Aufrecht, "Berl. klin. Woch.," Oct. 21, 1901. Baumgarten, "Wien. klin. Woch.," 1901, No. 2. Heymans, "Arch. de Pharmacodynamie et Therap.," tome xiii, p. 469. Roberts, "Lancet," March 29, 1902. Ribbert, "Deut. med. Woch.," April 24, 1902. Watanabe, "Ziegler's Beitr.," 1902, Bd. 31, p. 366. Esser, "Deut. med. Woch.," March 4, 1902. Schmörl, "Münch. med. Woch.," Aug. 19, 1902, p. 1379. Woodhead, "Report of the Henry Phipps Institute for the Study, Prevention and Treatment of Tuberculosis," Philadelphia, vol. i, 1904. Orth, "Berl. klin. Woch.," 1904, Nos. 11, 12, and 13. Owen, "Brit. Med. Jour.," April 2, 1904, p. 765. Perkins, "Med. News," April 16, 1904, p. 744. Blumer and Lartigau, "California State Jour. of Medicine," Sept., 1904. Swan, "Proceed. of the Phila. Co. Med. Soc.," Feb. 29, 1904, vol. xxv, n. s., vol. vi. Weber, "Lancet," April 2, 1904, p. 924. Brown and Pope, "Amer. Jour. of Med. Sci.," Oct 1904, p. 619. Abrikossoff, "Virchow's Arch.," 1904, Bd. 178, p. 173. Was-

phthisis, are names applied to the pulmonary manifestations of infection by the tubercle bacillus. The entrance of the tubercle bacillus into the pulmonary parenchyma may be manifested in a number of ways, depending upon the resistance of the individual, the virulence of the infecting organism, and the route of the infection, as well as upon the extent of bacterial distribution in the pulmonary tissue. It is, of course, in all its forms due to the tubercle bacillus.[1] The organism may reach the lung through at least three important avenues: (1) bronchi, (2) lymphatics, (3) blood-vessels, and possibly by direct invasion from adjacent tissues.

Aerogenous or *pneumatogenous infection* occurs through the inhalation of tubercle bacilli. It is probable that when the bacilli are deposited within the larger bronchioles, invasion of the peribronchial tissue is less likely to occur; and that when the tubercle germs escape extrusion by the activity of the ciliated epithelium and by expectoration, they may pass through denuded areas in the bronchial wall, reaching the peribronchial tissue, and eventually a lymphatic node, in which they give rise to tuberculosis. In other instances a primary tuberculous lesion is produced in the larynx, trachea, or larger bronchi, and, from these structures, invasion of the lymph-nodes or pulmonary parenchyma may occur.

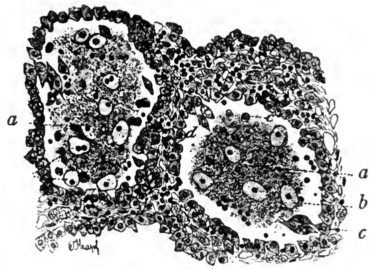


FIG. 302.—TUBERCULOUS PNEUMONIA. THE DESQUAMATIVE LESION WITHIN THE AIR-VESICLES WHICH OCCURS NEAR TO AND AROUND TUBERCLES IN THE LUNG, OR RESULTS FROM THE DEPOSIT OF THE TUBERCLE BACILLUS IN THE AIR-VESICLES.—(*Schmaus.*) × 250 diameters.

a, *a*. Exudate undergoing degenerative changes (caseation) in the air-vesicle. *b*. Round cells in same. *c*. Desquamating cells. The intervesicular walls are thickened.

From a primary tuberculous focus in the larynx, trachea, or larger bronchi, or from a tuberculous area in the lung, infected material may be aspirated into the smaller bronchi, or even into the vesicular structure. It is probably more common for the organism to reach the finer ramifications of the bronchioles when inhaled in the form of a fine dust. Watanabe and others have shown that no matter how the bacillus reaches the vesicular structure or the smaller bronchioles, a catarrhal inflammation results. At first this inflammation partakes of the character of an ordinary catarrhal process associated with desquamation of the epithelium and with accumulation of the catarrhal products in the vesicle, infundibulum, and smaller bronchiole. Within this inflammatory collection, growth of the tubercle bacilli is favored; instead of the catarrhal accumulation undergoing the usual softening and expulsion, caseation results, due to the specific action of the product of the tubercle bacillus. The progress that the change makes must depend largely upon the virulence of the organism and upon the susceptibility of the individual. It is probable that, with a high degree of immunity, the bacillus may at

sermann, "Berl. klin. Woch.," Nov. 28, 1904. Osler, "Brooklyn Med. Jour.," Feb., 1905. Von Ruck, "N. Y. Med. Jour.," March 11, 1905. Schwarz, "Centralbl. f. allg. Path. u. path. Anat.," April 15, 1905. Ophüls, "Trans. of the British Congress on Tuberculosis," 1901, vol. iii.

[1] See p. 144; also Morbid Anatomy of Tuberculosis, p. 149.

once be destroyed, and that the bacterial invasion of the vesicular wall may be arrested by the protective forces of the tissues.

When infection through the bronchi occurs, as just indicated, it is not necessary to presuppose any antecedent lesion. In a small percentage of cases, however, a bronchopneumonia, not of tuberculous origin, is infected by the tubercle bacillus. The result is essentially the same as though the lesion had been tuberculous from the start. Under favorable circumstances the inflammation is restricted to a small area of pulmonary tissue. The solidified nodule, commonly small, undergoes caseation and encapsulation by a wall of fibrous tissue, into which lime salts may be infiltrated. This constitutes the so-called quiescent,

FIG. 303.—LUNG, CHRONIC CASEOUS AND ULCERATING TUBERCULOSIS OF THE APEX; TUBERCULOUS BRONCHITIS, AND A MILIARY TUBERCULOSIS.

"healed-in," or cretaceous tubercle, and is what the older writers spoke of as chronic or caseous catarrhal pneumonia. With less evident resistance, or with more virulent infection, involvement of the bronchioles and of adjacent vesicular structures occurs. This is commonly preceded by more or less leukocytic invasion and proliferative change, which later terminate in necrosis and caseation. The process more or less rapidly involves the whole of the lobule in which the original infection occurred. When a lobule or part of a lobule has been infected, the area may be enlarged by the coalescence of adjacent lobules simultaneously involved, or it may extend from one lobule to another.

The gross lesion resulting from such infection must vary. As a

rule, in adults the structural change involves to a greater extent, and is most conspicuous in, the apex, although the lower lobes may also suffer. The point in the apex usually affected is from two to five centimeters below the superior border. Of the many explanations that have been advanced for the well-known frequency with which the apex is attacked, none is fully satisfactory. It is probable that the more active circulation and freer movement of the lower part of the lung may better enable the organ to expel the infectious material, and, by reason of its abundant blood supply, to resist infection. The lessened pulmonary movement at the apex offers better opportunities for the deposit of infectious material on the bronchial surfaces. Aufrecht and, more recently, Wassermann have suggested that the frequent involvement of the apices is due to the entrance of bacilli by way of the tonsils, pharynx, cervical lymph-nodes, and pleura. Aufrecht believes that the peribronchial nodes are infected from the cervical chain and that in this way the lung is reached. It is well known that even in minor lesions of the apex adhesions to the vault of the pleura are frequently present, and Wassermann construes this to be an evidence of direct infection of the lung from the cervical lymphatics. In adults involvement of the lower lobes is usually indicative of a primary lesion higher in the lung, from which the infected material has been aspirated into the more dependent portions.

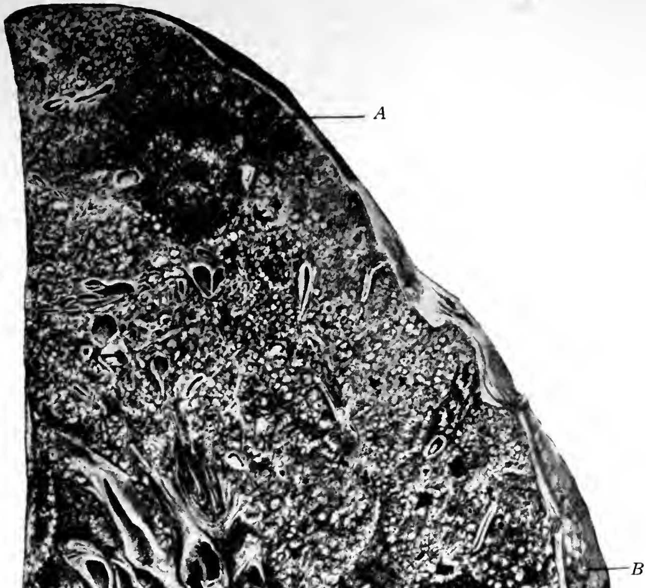
In many instances of pneumatogenous tuberculosis the process remains local, with the development of fibrous tissue in the surrounding structures, to which reference has already been made. In other cases the initial infection must have involved a number of areas in the pulmonary tissue, or a primary infection may have been followed by extension to adjacent lobules. These recognized differences possibly justify the terms (1) *localized*, *restricted*, or *chronic pneumatogenous* or *bronchogenic tuberculosis;* and (2) *disseminated*, *bronchogenic*, *tuberculous pneumonia*. The symptomatology of the conditions is vastly different, largely because of the greater amount of pulmonary tissue involved in the last-named process, but pathologically there is little difference except that due to the fact that the sudden appearance of a multitude of lesions must be taken as an evidence of weak resistance, and as this must of necessity further lessen the protective powers, the disease not uncommonly runs a rapid course.

With the inception of the initial lesion of tuberculosis in the pulmonary tissue,—if Wassermann's views are correct, the primary infection being lymphatic,—extension to adjacent intervesicular and interlobular structures occurs by means of the lymph paths, constituting a form of *lymphogenous* or *lymphogenic tuberculosis*. Thus, in many areas of purely bronchogenic tuberculosis of the kind described in the foregoing paragraphs, it is quite easy to recognize that the extension is taking place by means of the adjacent lymphatics. This view is further supported by the fact that the lymph paths through the pulmonary tissue are followed, and that, either primarily or secondarily, the lymph-nodes are eventually affected. Involvement of a lymph-node lying close to a blood-vessel—pulmonary artery, or vein—may be followed by extension into the vessel-wall, which later becomes caseous. In the vessel may be formed a thrombus in which caseation occurs, followed by the escape of infectious material into the blood stream. If the blood-vessel in-

volved be small, and the blood current be toward the periphery, as would be the case in the branches of the pulmonary artery, there is brought about a circumscribed *hematogenous miliary tuberculosis*. In other cases the infection of the pulmonary tissue through the blood stream is more uniform, as the result of a wider and more general distribution of the tubercle bacilli deposited from the circulating blood. In the circumscribed hematogenous tuberculosis one lung or a part of a lung may be involved, while in the general or diffuse hematogenous (miliary) tuberculosis there is usually a more or less uniform involvement of both lungs. Although it is the general belief that pulmonary tuberculosis is an aerogenous infection, the view is not without opposition. Ribbert and Baumgarten are ardent advocates of hematogenous infection, and the latter has been able to produce strictly localized pulmonary tuberculosis by infecting animals through the urethral mucosa. Aufrecht also inclines to the hematogenous origin of many cases. Woodhead strongly insists on the presence of some primary focus, usually catarrhal, on which the tubercle bacillus is engrafted. From such points of infection local dissemination occurs through the lymphatics. Abrikossoff thinks that the lesion begins as a peribronchial tuberculous lymphangitis which extends along the wall of the bronchi. As a result of caseation the bronchial wall is opened and the caseous material aspirated into other parts of the organ, causing areas of bronchopneumonia which progress to caseation. In the completely evolved tuberculosis of pulmonary tissue, bronchogenous, lymphogenous, and hematogenous distribution of the organism may often be implicated.

Morbid Anatomy.—There is probably no other well-known affection of the lung associated with more diversity in the gross lesions, and yet due, in all its forms, to the same cause. In some of the cases it may be possible to formulate an opinion as to the method by which infection occurred. In other cases this is quite impossible. Usually, it is said that, anatomically, tuberculosis of the lung manifests itself in three forms: (1) An acute miliary tuberculosis, also called acute phthisis, or galloping consumption; (2) chronic ulcerating or caseous tuberculosis; (3) fibroid phthisis.

The morbid anatomy of **acute miliary tuberculosis of the lung** (Plate XVI.) must depend upon the extent and duration of the tuberculous process; organs in which there has been a wide-spread distribution of a large number of tubercles do not manifest the same changes as those in which the eruption involves a more restricted area and gives rise to fewer tubercles. Sometimes the large number of tubercles, with the associated proliferative changes, may almost as fully solidify a lung as does croupous pneumonia and, both clinically and pathologically, the organs may closely resemble each other. If the process has existed for even a comparatively short time, the miliary tubercles become sufficiently large to be readily recognized, and, of course, as soon as this occurs the anatomic diagnosis is easily made. The lung is more voluminous than normal, and does not collapse with its wonted readiness. The pleura is frequently the seat of an old inflammation, and not uncommonly shows uniform adhesion between the visceral and parietal layers. Small tubercles may be seen in the pleura or just beneath, or, what is more common, they are palpable. On incision, the lung usually cuts with more resistance than normal. The amount



LUNG (SECTION). ACUTE MILIARY TUBERCULOSIS FROM A CASE OF GENERAL MILIARY TUBERCULOSIS.

A. Area of diffuse interstitial hemorrhage. *B*. Subpleural tubercles showing through the thickened pleura. *C*. Thickened pleura partly detached from lung.

of moisture is dependent upon the presence of an associated edema, intense congestion, or hyperemia. The recognizable tubercles are usually paler than the surrounding lung tissue, and may be white, grayish-white, or yellow in color.[1]

With the acute lesion, evidences of older tuberculosis, such as healed-in areas, areas of caseation and fibrosis, or fully formed cavities, may be present. It may be possible to demonstrate the primary nodule from which infection has occurred, although in the large majority of cases the demonstration will be unsatisfactory, and seldom conclusive.

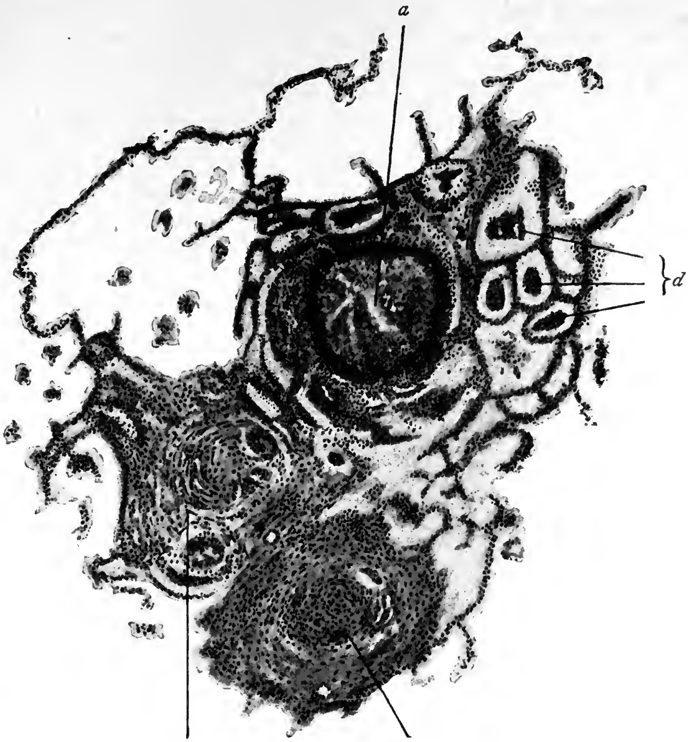


Fig. 304.—Tuberculosis of the Lung.

Tissue fixed in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin, and mounted in balsam. *a*. Tubercle with advanced caseation. *b* and *c*. Tubercles showing less advanced degenerative changes. In the upper and right quadrant of *b* is seen a giant cell. *d*. Three air-vesicles partly filled by inflammatory products, tuberculous pneumonia. (¼-inch objective, 1-inch ocular.)

An examination of the lung during the period in which the tubercles are forming, or when they are fully formed, will result in the recognition of histologic changes such as are shown in figure 84, page 151. (See also Fig. 304.) In acute cases there is usually considerable catarrhal pneumonia or intravesicular exudate, and sometimes this may be fibrinous, further explaining the gross resemblance of the lesion to croupous pneumonia.

[1] See Tuberculosis, p. 144; also Morbid Anatomy of Tuberculosis, p. 149.

Morbid Anatomy of the Chronic Ulcerating, Ulcerative, or Caseous Tuberculosis of the Lung.—This is a type of the disease that usually follows aerogenous infection. The structural changes are commonly situated in the apex, although other parts of the lung may be involved. The lesion consists for the most part of caseous areas, varying in size from purely microscopic bodies (miliary tubercles) to cavities from five to ten centimeters in diameter, or much larger. The cavity formation is brought about by caseation and confluence of a large number of tubercles, with an associated bronchopneumonia, which itself becomes caseous, and is, of course, due to the tuberculous infection of the pulmonary tissue. As these areas of caseation increase in size by peripheral extension and coalescence, obliterative changes take place in the blood-vessels, the vesicular walls and fibrous septa disappear before the extending necrosis, the pulmonary tissue itself becomes caseous, and eventually the necrotic collection ruptures into a bronchus. With evacuation of the caseous contents a cavity is formed. The wall of such a cavity is lined by a layer of necrotic and caseating pulmonary tissue containing tubercles in various stages of caseation, and the inflammatory products that usually accompany infection by the tubercle bacillus. External to the caseous layer is a wall of granulation tissue composed largely of lymphoid cells, and usually containing easily recognizable tubercles. Outside of the zone of granulation tissue is a variable amount of fibrous tissue. In chronic cases cavities of long duration are sometimes surrounded by a fibrous membrane the inner surface of which may be smooth or granular, usually the latter. Such excavations resemble dilated bronchi, and the two may be present in the same organ. The points assisting in differentiating the two cavities have been mentioned on p. 580.

The most disastrous changes in pulmonary tuberculosis result from *secondary infection by pyogenic organisms.* Ophüls found that in twenty of thirty-nine cases of pulmonary tuberculosis, acute mixed infection, or sepsis, seemed to be the immediate cause of death. He has not been able to corroborate the observations of those who maintain that the softening observed in tuberculous lesions is invariably due to mixed infection. Comparative pathology shows that in the lower animals, particularly cattle, rapid and extensive necrosis is usually due to concurrent pyococcic invasion of the tuberculous tissue. In such cases and in man the bacteria accompanying the tubercle bacillus in the lesions are the ordinary pyogenic cocci, the pneumococcus, tetracoccus, colon bacillus, and occasionally other microbes, all of which may not be pyogenic. Whether or not such organisms find ready access to the caseous area before its rupture into the bronchial wall, their introduction is assured at this time, and hence there are added to the tuberculous process, properly so called, active pyogenesis and the absorption of the products of pyogenic bacteria. The progressive extension of caseous tuberculosis is favored by the occurrence of mixed infection. Necrotic changes in the contiguous tissue and involvement of the adjacent lymphatics may progress slowly. In other instances there is a more rapid extension, and, after a comparatively short period of cavity formation, invasion of a blood-vessel or prominent lymph canal occurs, or the process extends to other parts of the lung, and leads to the rapid dissemination of infection and to death.

Morbid Anatomy of Fibroid Phthisis.—The term fibroid phthisis is applied to tuberculous processes involving a lung where the tendency is toward fibrosis, restriction, limitation, and healing-in, and where necrosis, degeneration, and extension are limited by the protective powers of the tissues or are rendered less extensive by reason of reduced

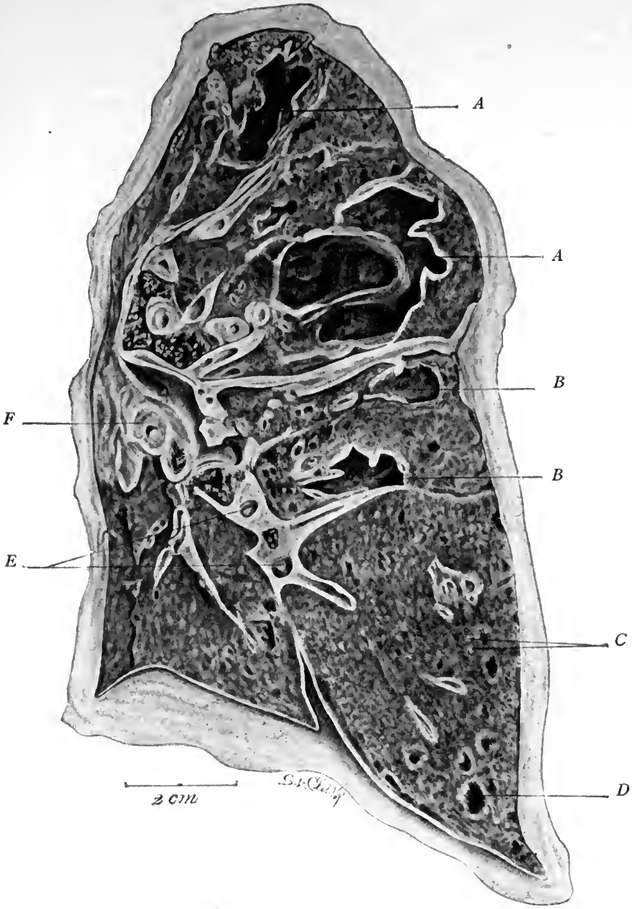


FIG. 305.—LUNG, CHRONIC ULCERATIVE TUBERCULOSIS OF UPPER LOBE; ACUTE MILIARY TUBERCULOSIS AS A TERMINAL LESION INVOLVING THE ENTIRE ORGAN; SLIGHT INTERSTITIAL (FIBROID) PNEUMONIA; CHRONIC TUBERCULOUS PERIBRONCHITIS; BRONCHIECTASIS; ACUTE PSEUDOMEMBRANOUS BRONCHITIS; CHRONIC FIBROHYALOPLEURITIS.

A, A. Cavities. *B B.* Dilated bronchi. *C.* Miliary tubercles, many of which are conspicuous, especially in the lower lobe. *D.* Area of hemorrhage. *E.* Two bronchi containing casts. *F.* Bronchus, the wall of which is greatly thickened by a tuberculous peribronchitis.

virulence of the infecting organism. In typical cases a comparatively small area of the lung is involved. In the purely tuberculous lesion a large portion of the organ may show the changes of fibroid pneumonia, and contain only a small amount of caseous tissue. In other cases the evidence of tuberculosis, at present active or quiescent, may be ir-

regularly distributed through a large part of the pulmonary tissue. In typical cases the evidence indicates that tuberculosis is being limited or restricted by fibroid and calcareous changes; in other words, that healing-in is progressing. In patients dying from other causes small areas are not infrequently found in which the tuberculous process has been fully restricted or walled off by masses of fibrous tissue, or limited by calcareous infiltration. (See Quiescent Tuberculosis, p. 151.)

Mixed Forms of Pulmonary Tuberculosis.—In a large percentage of the cases of tuberculosis of the lung, as observed postmortem, the disease is manifested by mixed lesions, due to the presence of more than one form of tuberculosis, as described in the foregoing pages. There is not

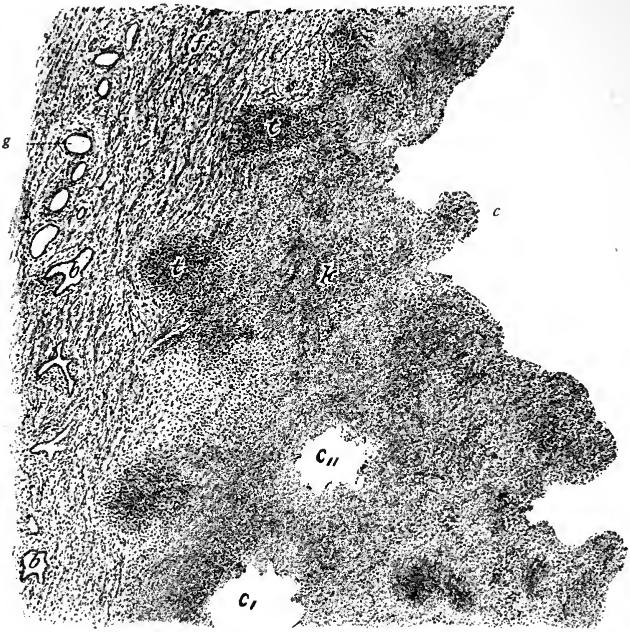


FIG. 306.—WALL OF A TUBERCULOUS CAVITY.—(*Schmaus.*) × 100 diameters.
c. Cavity. c_i, c_{ii}. Smaller cavities that will, eventually, as the result of caseation and liquefaction of the intervening tissue, blend with the larger cavity. *b, b.* Remains of a bronchus. *t, t.* Tubercles undergoing softening. Just over *a* are shown other tubercles. *k.* Caseous wall. *g.* Blood-vessel.

infrequently a distinct area in which the lesion is old and cretaceous. Around this, at times some distance from it, can be recognized a more recent and active tuberculosis, with cavity formation, and corresponding to the anatomic subdivision—chronic caseous tuberculosis. Still other parts of the lung may show the changes of a typic acute miliary tuberculosis.

Tuberculosis of the lung in all its forms is practically always associated with some lesion of the overlying pleura, which may be a frank, acute pleuritis[1] or chronic sclerotic change. Frequently the cavity of

[1] See Inflammations of the Serous Membranes, p. 475.

the pleura has been obliterated by universal adhesions and often the serosa is enormously thickened (chronic hyperplastic hyaloserositis).

Syphilis of the lung[1] occurs in both the *congenital* and *acquired* forms of the disease. In the former a condition known as *white hepatization* is occasionally seen; proliferation of the cells that line the fetal vesicles and of the connective tissue of the septa leads to the obliteration of the air-spaces, and when, at birth, the inspired air enters the lung, none gains ingress to the affected area; the only circulation to this part is that for supplying nourishment; hence, the area is pale, anemic, and is said to show *white hepatization*, the paleness contrasting with the surrounding hyperemic area. Another manifestation of transmitted syphilis is the ordinary gumma. This may be found in any part of the lung, but is usually near the larger bronchi at the hilum. The gummata are for the most part small, but they may attain diameters of from two to six centimeters. Gummata of the lung in congenital syphilis are of infrequent occurrence, but when fully developed, they do not differ essentially from those found in the acquired disease.

In *acquired syphilis* gummata are more frequent; the situation is usually at the root of the lung, but they may be anywhere. They are gray or grayish-yellow, not uncommonly caseous, and surrounded by a fibrous capsule, which, if recent, is translucent; if older, is firm, truly fibroid, and dense. Like all the infective granulation tumors, these begin in the alveolar walls or in the walls of the bronchi, beneath the basement membrane; after the aggregation of cellular elements hyaline degeneration and necrosis ensue, and eventually caseation completes the process, and evacuation into a bronchus commonly follows.

Occasionally, an interstitial pneumonia accompanies the formation of the gumma, and Virchow believed that a purely syphilitic process may begin as an interstitial inflammation at the root of the lung and extend along the course of the interlobar and the interlobular septa, particularly the latter. When marked, it may be attended by bronchiectasis and all the usual phenomena of interstitial pneumonia. In many cases of acquired pulmonary syphilis a catarrhal inflammation involving the bronchi and vesicles accompanies the interstitial fibroid hyperplasia or the formation of gummata. The clinical and even the anatomic changes may resemble tuberculosis so closely that nothing short of demonstrating the tubercle bacillus can enable the observer to identify the process. As syphilitics may become tuberculous and patients with tuberculosis may acquire syphilis, the affections may be concurrent in the lung.

Leprosy of the lung may occur as a distinctly miliary process, the leprous nodules so closely resembling those of tuberculosis that many claim the determining factor is a tuberculous infection of a leprous individual; the almost utter impossibility of differentiating the lesions has led a few to believe that leprosy was but a form of tuberculosis; evidence confirmatory of this view is not in the least conclusive, and for

[1] Flockemann, "Centralbl. f. Path. u. path. Anat.," 1899, Bd. x, p. 449. "Nothnagel's Encyclopedia of Practical Medicine," American edition, article on "Syphilitic Pneumonia," vol. on "Diseases of the Bronchi, Pleura, and Lungs," 1903, p. 643. Winfield, "Med. News," Aug. 30, 1902, p. 405. Hansemann, "Centralbl. f. med. Wiss.," July 5, 1902. Berg, "Med. Record," Dec. 13, 1902, p. 926. Remsen, "Bull. of Johns Hopkins Hosp.," Oct., 1903, p. 280. Willson, "Med. News," Feb. 25, 1905, p. 351.

the present there seems to be no reason for believing that the two diseases are in any way related.

Glanders of the lung[1] may arise as the result of aspiration of the bacilli from lesions in the upper passage, or, as in acute glanders, the infection may occur by the blood stream. Once localized in the lung tissue, whether interstitial or intravesicular, a more or less severe bronchopneumonia is brought about, and frequently this proves fatal. When time is afforded, the typical glanders nodules develop. These lie, as a rule, immediately under the pleura, and present somewhat different aspects at different stages of their development. At first they are gray, slightly translucent, and much softer than tubercles; later they become somewhat denser, and a hyaline change occurs in the center, the process eventually terminating in a caseous-like, encapsulated mass, especially if the lesion be restricted to one or two points of infection in an animal not very susceptible to the disease. In the horse, in which animal susceptibility is marked, and occasionally in man, the condition terminates in a suppurative pneumonia by pyogenic infection of the glanders nodules.

Actinomycosis of the lung[2] results, in most cases, from infected material reaching the involved part through the air-passages; a bronchial inflammation accompanies the fungus down into the lobules, where a so-called miliary bronchopneumonia ensues; the number of these areas is dependent upon the number and dissemination of the fungi. A mass of granulation tissue develops around the point of infection, in which also occur characteristic groups of fungi. Suppuration and not uncommonly cavity formation ensue; it is usually conceded that the ray fungus is itself pyogenic, and can, therefore, induce pus-formation without the intervention of the cocci of suppuration. When the actinomycotic lesion approaches the surface, an adhesive pleurisy usually results, and progresses to obliteration of the cavity. In many of the reported cases the suppurative process penetrated the chest-wall and the diagnosis was made by finding the characteristic granules in the discharge. Mediastinal actinomycosis may or may not accompany the pulmonary form, or the one may be secondary to the other. Occasionally, actinomycotic fibroid changes in the lung and "healing-in" of the infected area occur. In such cases the masses found postmortem are surrounded by a dense fibrous and calcareous capsule. The diagnosis of actinomycosis, both clinical and pathologic, is dependent upon finding the fungus in the sputum during life or in the masses postmortem. Forms of actinomycotic bronchitis and peribronchitis have been described.

Tumors of the lungs[3] are rarely primary; usually they arise by

[1] MacCallum, "Ziegler's Beitr.," 1902, Bd. xxxi, p. 440. See also Glanders, p. 160.

[2] Spijariny, abstract in "Med. Record," April 11, 1903, p. 576. Webber, "Brit. Med. Jour.," May 9, 1903, p. 1084. See also "Pulmonary Streptothricosis," Warthin and Olney, "Amer. Jour. of Med. Sci.," Oct., 1904, p. 637. Maass, "Annals of Surgery," Aug., 1903, p. 292. Also consult Actinomycosis, p. 166.

[3] Pollack, "Virchow's Arch.," 1901, Bd. 175, p. 129. Musser, "Univ. of Penna. Med. Bull.," 1903. Ramond and Boidin, "La Presse Méd.," Jan. 14, 1903, p. 56. Rolleston and Trevor, "Brit. Med. Jour.," Feb. 14, 1903, p. 361. Demorest, "Med. Record," Jan. 16, 1904, p. 96. Bremken, "Amer. Jour. of Med. Sci.," Dec., 1903. Adler, Carpenter Lecture, N. Y. Acad. of Medicine, Oct. 20, 1904. Broc, "C. R. de Soc. Anat.," Jan. 27, 1905. Packard, "Med. News," Feb. 18, 1905, p. 303.

metastasis from other organs or by invasion from adjacent structures. According to Adler, Wolff observed 46 primary tumors of the lung in 20,160 autopsies. Adler collated 330 cases of lung tumor; 211 were cancers, 22 sarcomata, and 24 endotheliomata; 10 were mixed tumors and the remainder unclassified. Occasionally the presence of pulmonary neoplasms may be diagnosed by the examination of fragments found in the expectoration; in discussing Broc's case, Cornil referred to such an instance, and Demorest also records a case in which the diagnosis was made from the sputum. Non-malignant epithelial tumors of the lung are exceedingly rare, although adenomata of the bronchial glands have been described. Embryonic epithelial neoplasms are not correspondingly rare: I have seen four instances within the last few years. When carcinomata occur in the lung, as the result of the rich vascular supply and the relatively small amount of connective tissue, the neoplasm is usually encephaloid. The growth may be circumscribed and manifest itself as a few masses, or it may consist of one gray or white soft nodule. Each nodule may develop as a single mass without very marked dissemination, but more commonly extension occurs through the lymph-channels, and results in disseminated growths throughout the lung tissue. The local metastasis gives rise to nodules similar to the original, which, by extension, coalesce and convert nearly all, if not all, the lung into a cancerous mass. Invasion of peribronchial and mediastinal lymphatics takes place, and if not fatal by this time, the process may extend to the opposite organ.

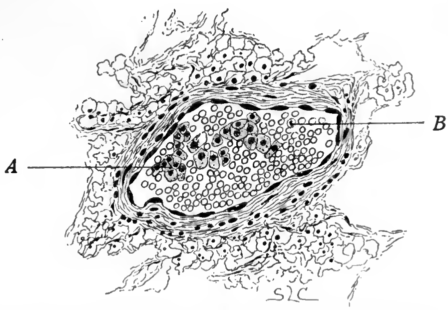


FIG. 307.—BRANCH OF PULMONARY ARTERY CONTAINING SARCOMA CELLS FROM A CASE OF WIDE-SPREAD DISSEMINATION OF A TUMOR PRIMARY IN THE SUBCUTANEOUS TISSUE OF THE THIGH.

A Sarcoma cells. *B*. Polymorphonuclear leukocyte. There is some irregularity in the size and shape of the red cells due to the associated secondary anemia.

Primary tumors of the adult connective-tissue series are less frequent. *Fibroma*, *chondroma*, *osteoma*, and mixed forms of these, with, rarely, a small quantity of *lipomatous* tissue, have been described. They are commonly multiple; usually, a number are to be found disseminated throughout one or both lungs.

Embryonic connective-tissue neoplasms (*sarcomata*) are infrequent primary tumors of the lung. The form of sarcoma known as *endothelioma*, arising in or from the pleura, is the most common. Like the cancers, such tumors usually form single large masses, but may extend to the lymph-nodes and mediastinal tissues. As a rule, primary sarcoma is restricted to one lung.

Secondary tumors of the lung arise as the result of invasion through the lymphatics or the blood; even the instances of apparently direct invasion are not truly so. The embryonic epithelial tumors—the cancers—invade the lung, as secondary growths, in a very small percentage of the cases of carcinoma elsewhere. The epitheliomata rarely, if ever, the scirrhus more commonly, and the encephaloid most frequently,

occur as secondary growths in the lung. The cancers, spreading by the lymphatics, usually involve those structures in the lung first, and manifest dissemination along the course of the lymph-channels. Reaching the pleura by the lymphatic system, dissemination may occur along the course of the interlobular lymph-vessels, in which will be seen the grayish cancerous lines traversing the connective-tissue septa, and even extending to the peribronchial lymph-nodes.

Carcinoma occasionally reaches the lung by the blood, and the frequency with which this is associated with an initial focus in the digestive organs, more especially that part of the alimentary canal that communicates with the chyle duct, apparently explains this form of dissemination; in reality, the cancer cells have reached the blood by being poured into the venous circulation through the lymph-chan-

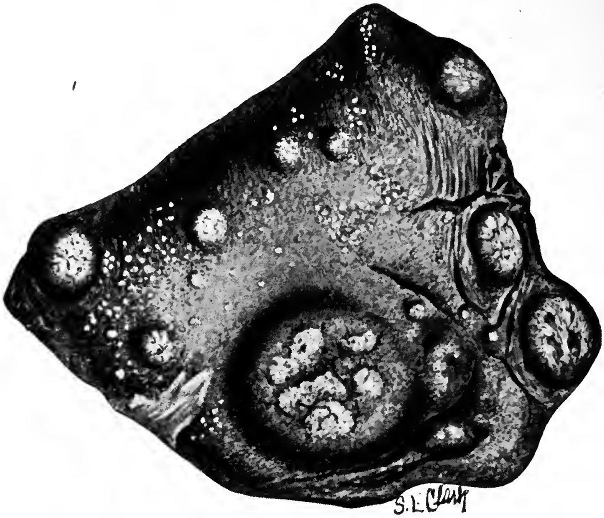


FIG. 308.—LUNG, PART OF SEROUS SURFACE; SECONDARY SARCOMA.
The larger, distinctly elevated masses are the oldest; similar smaller nodules are more recent, while the youngest growths are shown as minute (miliary) grayish-white or white subserous dotlets. The specimen is a part only of the lower lobe; reproduction natural size. The incised surface of the same specimen is shown in Fig. 309.

nels arising in the abdominal cavity. When a cancerous embolus lodges in the lung, the growth immediately proceeds in the usual way; as these emboli are commonly multiple and are fairly abundant, both lungs are likely to be involved, and many small tumors occur more frequently than a single large one. There can be found, of course, no regularity in their location, and, once lodged, they follow the same processes of growth and local dissemination that have already been indicated; the encephaloid is the carcinoma most frequently reaching the lung by metastasis; encephaloid cancers that have undergone colloid or mucoid change are especially liable to such dissemination. Scirrhus rarely involves the lung.

Of the secondary tumors belonging to the adult connective-tissue

series, there are fourteen recorded instances in which chondromata and osteomata have reached the lung. By hematogenous dissemination the sarcomata are the most frequent invaders of the pulmonary tissues. This is due to the relation which the cellular elements of these neoplasms bear to the blood channels which they contain. The small round-cell varieties are most commonly noted, although any form of sarcoma may be disseminated by the blood. As to the seat of the initial growth, it is found that the sarcomata arising in bone, and especially in the long bones, are the most frequent as secondary growths in the lung. Melanotic sarcomata are also prone to such metastasis. Unlike cancers, sarcomata, if situated in the distribution of the portal vein, rarely reach the lung, but, traveling by the blood-vessels, involve the liver.

Parasites in the lung and bronchi are not of frequent occurrence. Reference has already been made to the Distoma westermanii, distoma pulmonale, or bronchial fluke, as a cause of hemoptysis. (See p. 192.) Ascaris lumbricoides occasionally migrates into the air-passages, and may cause obstruction with fatal results; or, reaching the bronchi, may induce gangrene, etc. It is not uncommon in infested bodies to find that the worm has entered the air-passages postmortem.

Fig. 309.—Lung, Incised Surface of Part of One Lobe, Secondary Sarcoma.
The serous surface is shown in Fig. 308. (Natural size.)

Hydatids[1] occur in the lung; they may be central or subpleural. The subpleural form, and hydatids of the pleura, may occur together; in either case effusion into the pleura is usually found, and not uncommonly empyema results. The cysts are multiple and commonly are near the base; they may be diaphragmatic. When in the lung, the compression resulting from their growth leads to conditions favorable to infection, and abscess and gangrene sometimes result. Clinically and pathologically, a positive diagnosis is dependent upon finding the booklets in the cysts or discharges. (See p. 199.) The parasites more rarely found in the lung are the Cysticercus cellulosæ, Strongylus longevaginatus, and Pentastoma denticulatum.

[1] Pel, "Berl. klin. Woch.," Aug. 26, 1901. Lendon, "Clinical Lectures on Diseases of the Lung," 1902. Quill, "Jour. of Royal Army Med. Corps," April, 1904. Symmers, "Lancet," Jan. 7, 1905, p. 22.

CHAPTER IX.

DISEASES OF THE URINARY ORGANS.[1]

The Normal Kidney.—The kidneys vary somewhat in size and are rarely symmetric; normally the left kidney weighs 150 gm. to 190 gm., and the right slightly less. According to Verraeck,[2] the specific gravity

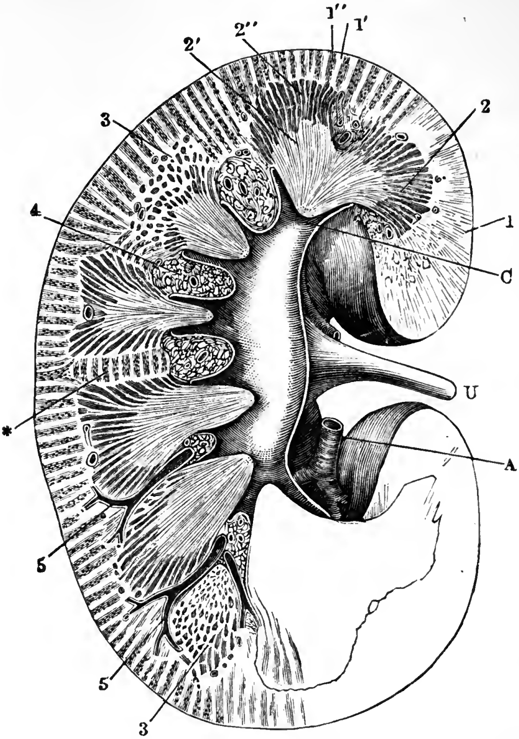


FIG. 310.—LONGITUDINAL SECTION OF THE KIDNEY.—(*Tyson, after Henle.*)
1. Cortex, equal in thickness to about one-half the length of the medullary pyramid. 2. Medulla. C. Pelvis, with calices extending outward between the papillæ of the pyramids. 1'. Medullary rays, between which are the labyrinths 1''. 2'. Conducting tubules of the medulla. The line from 2'' runs to a point just below the corticomedullary line. A. Renal artery: at 5, 5 is shown its method of distribution. 3. 3. Transverse section of tubules. 4. Fat of renal pelvis. *Transversely coursing medullary rays. U. Ureter.

of the organs varies between 1.050 and 1.055. The pyramid is the anatomic unit; the Malpighian tuft, with its blood-vessels and the tube

[1] Of the more recent works on diseases of the kidney the student is advised to consult Morris, "Surgical Diseases of the Kidney and Ureter," 1901, and Tyson, "Bright's Disease and Diabetes," 1904.
[2] "La Semaine Méd.," Aug. 7, 1901.

passing off as the proximal convoluted tube, the loop of Henle, the second or distal convoluted tube, and terminating in the conducting tube, constitutes the gland unit.

Histologically, the tubules are tracts of mucous membrane in which different portions are lined by epithelial cells having slightly different characters. The epithelium of the tuft is flat, with a tendency to cuboid outline; the epithelium of the convoluted tubes is more or less polyhedral. The cortex of the organ is made up of two histologic structures, which are most important from a pathologic standpoint; these are the labyrinth and the medullary rays or pyramids of Ferrein. In a perfectly normal kidney these two elements can not be satisfactorily differentiated by the unaided eye; but with the occurrence of inflammation or of marked degenerative change the structures named are often outlined with remarkable clearness. The thickness of the cortex varies considerably in health, and also depends on the size and general contour of the organ. A kidney may be short, with a thick cortex, or long and the cortical portion somewhat thinner; there is, however, a more or less definite relation between the cortex and the medullary portion, which is sufficiently constant to be utilized for comparison. If a pyramid be selected which is incised from apex to base, and a line be extended from the apex of the pyramid to the capsule, it will be found that two-thirds of the line rests upon the medullary portion, or the pyramid, and one-third upon the cortex; this relative proportion between the two parts is not absolute, but the variations are so slight that the rule is generally applicable, and, by applying this method of measurement, one can usually determine, at least approximately, whether the cortex is normal in thickness.

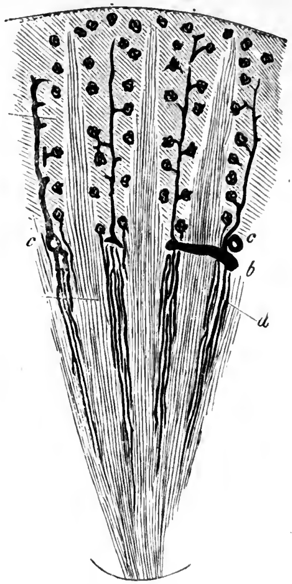


FIG. 311.—DIAGRAM OF BLOOD SUPPLY TO KIDNEY.—(*Rindfleisch.*)

b. Artery at the corticomedullary line, the same as 5 in figure 310. *c, c.* Blood-vessels passing upward to Malpighian tufts in the cortex. *d.* Blood-vessels passing downward into medulla. The diagram also shows the pyramids of the cortex, between which are the labyrinths containing the Malpighian tufts and convoluted tubules.

Malformations and Malpositions of the Kidney.[1]—It is necessary to consider these conditions together, as malformed kidneys are not, as a rule, in their normal positions. Abnormalities in form or position of the kidney are not infrequent. The commonest of all malpositions is that known as movable kidney, which is

[1] Cragin, "Amer. Jour. of Obst.," July, 1898. Blumer, "Albany Med. Annals," Jan., 1901. Preindlsberger, "Wien. klin. Rundschau," March 31, 1901. Guiteras, "Monatsberichte d. Urologie," Bd. ix, H. 7, p. 445. Hohmeier, "Zeit. f. Geb. u. Gyn.," vol. 51, No. 3. Rorie, "Brit. Med. Jour.," April 27, 1901. Gould, "Amer. Jour. of Med. Sci.," March, 1903. Morris, "Surgical Diseases of the Kidney and Ureter," 1901. Horton, "Northwest Medicine," April, 1903, p. 198. Cathelin, "Annal. des Mal. Genito-Urin.," vol. xxi, No. 23. Moore, "Jour. of Anat. and Phys.," London, 1903, vol. xxxviii, p. 99. Hamann, "Jour. of Med. Research," June, 1902, vol. viii, p. 125. Oberndorfer, "Münch. med. Woch.," March 10, 1903, p. 426. Engstron, "Zeit. f. klin. Med.," 1903, vol. 49. Tail-

generally an acquired condition, although authorities are agreed that the organ may be more movable than normal even at birth. Morris's statistics show that horseshoe kidney occurs about once in 1000 cases; absence, extreme atrophy, or dwarfing of one kidney, once in 2650 cases. The typic solitary organ resulting from fusion of two kidneys is found once in 16,000 postmortems. A single kidney is more frequent. According to Winter,[1] seven such organs have been removed by surgeons. Anomalies in the blood supply of the kidney are not uncommon; I have repeatedly observe two renal arteries, and three are notdinfrequent.

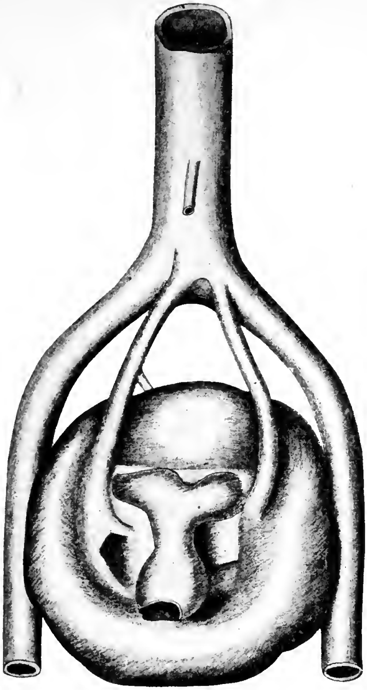


FIG. 312.—SOLITARY KIDNEY. (Anterior view.)

A. Aorta. The small branch between *A* and the bifurcation of the aorta is the inferior mesenteric artery (?). *B*. *B*. Common iliacs. It will be observed that the two renal arteries appear to come off directly at the bifurcation of the aorta. *C*. Kidney. Just above the letter *C* is the ureter. Posteriorly, the organ is slightly lobulated. Absence of renal tissue between the two renal arteries would convert this mass into a horseshoe kidney.—(*Drawing from specimen in the Museum of the Jefferson Medical College.*)

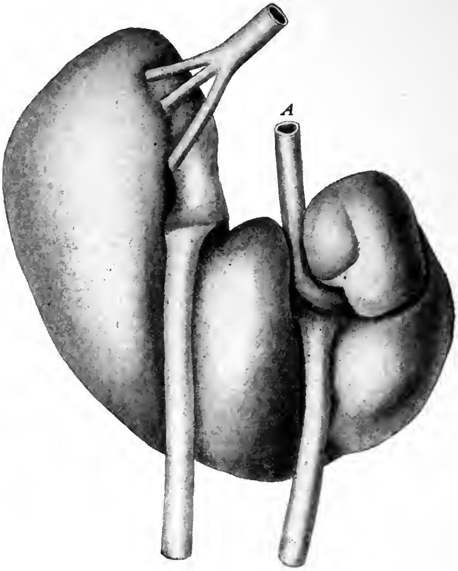


FIG. 313.—HORSESHOE KIDNEY. (Anterior aspect.)

A, *A*. Renal arteries. *B*, *B*. Ureters. In this particular case the two ureters pass downward to the bladder and enter separately. The end of the organ to the right shows considerable lobulation, such as is normal in fetal life, but usually absent in the fully formed kidney of the adult.

The **solitary kidney** represents a fusion of the two organs and their development as a single mass. As a rule, the solitary kidney possesses

hefer, "Soc. de Chir.," Oct. 28, 1903. Decherd, "Amer. Jour. of Med. Sci.," Jan., 1904. Cotton, "Arch. of Pediatrics," April, 1904. Dick, "Trans. of Chicago Path. Soc.," May 9, 1904. Wood-Jones, "Brit. Med. Jour.," Dec. 17, 1904. Pohlman, "Amer. Med.," 1904, vol. vii, No. 25, p. 987; also "Bull. Johns Hopkins Hosp.," Feb., 1905, p. 49.

[1] "Arch. f. klin. Chir.," 1903, lxix, No. 3.

a duplicated blood supply; it lies in the median line or slightly to one side, and is very much nearer the pelvis than the normally placed organs; indeed, it may be on the border of or even within the pelvic cavity. Commonly, there is but one ureter, although there may be two ureters or a single ureter dividing into two before it reaches the bladder, or two ureters uniting to form one just before the bladder is reached. The organ is likely to be floating, although it may be firmly attached. Ring or "disk-shaped" kidney is a malformation intermediate between the solitary and horseshoe forms.

Horseshoe Kidney.—Next to the solitary kidney, in degree of malformation, is the horseshoe kidney. In this condition the two kidneys

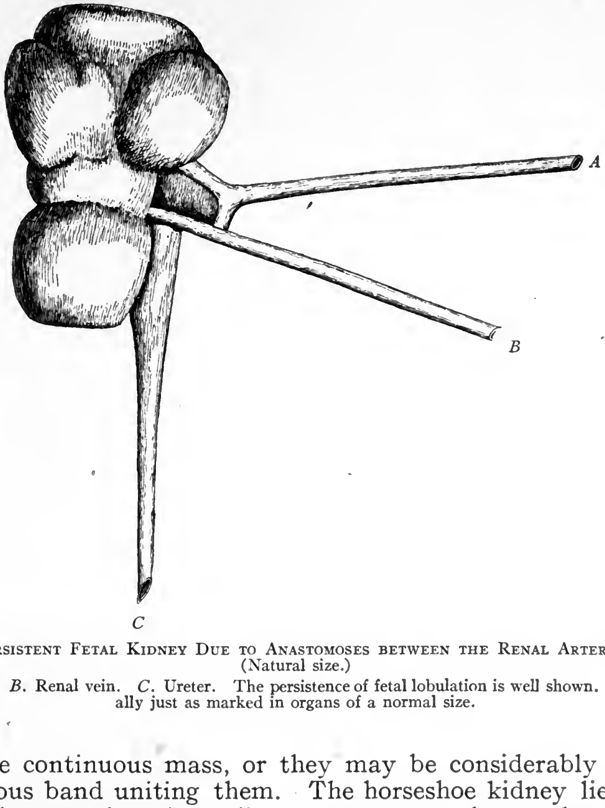


FIG. 314.—PERSISTENT FETAL KIDNEY DUE TO ANASTOMOSES BETWEEN THE RENAL ARTERY AND VEIN. (Natural size.)

A. Renal artery. *B*. Renal vein. *C*. Ureter. The persistence of fetal lobulation is well shown. It is occasionally just as marked in organs of a normal size.

may be one continuous mass, or they may be considerably separated with a fibrous band uniting them. The horseshoe kidney lies with its convexity downward, and usually possesses two pelves and two ureters; very rarely, such organs are placed to one side of the median line. The renal blood-vessels are usually abnormal, in that they arise from or join the larger blood-vessels lower than in health.

A **single kidney** is one essentially normal organ possessing the usual blood supply. It is alone because of developmental arrest and consequent absence of the opposite organ, and differs from the solitary kidney in that it does not, histologically or anatomically, although it may physiologically, represent the two organs. It is usually in the normal

position, but, having enlarged, its increased weight sometimes leads to loss of anchorage, and, consequently, to some form of acquired malposition.

Absence of the Kidney.—Rarely, both kidneys may be absent; absence or marked hypoplasia of one kidney is not so uncommon. Usually, it is the left kidney that is missing; the remaining organ hypertrophies and performs the function of two kidneys. The kidneys are not uncommonly lobulated, retaining this characteristic of fetal life. In exceptional cases a third kidney is present. The organ may be near one of the normally placed kidneys, but more commonly is situated lower in the abdominal cavity and possesses its own ureter and blood supply. The division of one kidney into two or more parts, receiving their blood supply from the same vessel and draining into the same ureter, does not really constitute an example of accessory or multiple organs.

Nephroptosis,[1] ren mobilis, or prolapse of the kidney, may be a part of a malformation, as already stated when considering solitary and horseshoe kidneys. In other cases it is distinctly an *acquired malposition.* Over eighty per cent. of the misplaced kidneys are found in women, in whom the condition is common. The frequency estimated by different writers varies: Küster states that 4.44 per cent. of all women consulting him have movable kidneys; Goelet and also Edebohls find that 20 per cent. of women are affected; Harris states that 56 per cent. possess movable kidneys. The morbid condition is most frequent during adult life,—between twenty and forty,—but is also seen in children and infants. The right kidney is the organ involved in over eighty per cent. of the cases, and in practically all the rest both are movable. The displacement commonly follows pregnancy or other conditions that tend to bring about an abnormal flaccidity of the abdominal walls. It is frequently associated with morbid processes that increase the size and weight of the kidney. Nephroptosis may be coincident with enteroptosis or prolapse of other viscera. It is said to be favored by absorption of the perirenal fat and abnormal length of the renal vessels. Trauma, in the form of blows and falls, may displace the organ. Tight lacing is assumed to be a cause. Pressure upon the liver, induced by stays, is transmitted to the kidney, which is thereby forced from its normal position.

The degree and, to a certain extent, the character of the mobility vary in different cases. The organ may be mobile behind the peritoneum, constituting the so-called **movable kidney;** Morris and others are inclined to recognize different degrees of movable kidney based upon the extent of the mobility. Morris also recognizes a condition in which the retroperitoneal organ may be displaced either vertically or laterally in a "cinder-sifting manner," but is not prolapsed forward. In other cases the kidney falls forward, bringing with it the peritoneum, thereby

[1] Morris, "Lancet," Nov. 30, 1901. Hutchinson, "Practitioner," Feb., 1902. McWilliams, "Med. News," Oct. 4, 1902, p. 625. Cabot, "Boston Med. and Surg. Jour.," March 6, 1902. Dupoux, "Thèse de Paris," 1902. Phillips, "Lancet," March 14, 1903, p. 731. Bonney, "Edinburgh Med. Jour.," Dec., 1902. Aaron, "Amer. Med.," Dec. 5, 1903, p. 893. Harris, "Jour. Amer. Med. Assoc.," June 1, 1901, also Feb. 13, 1904, p. 411. Treves, "Practitioner," Jan., 1905, p. 1. Macalister, "Allbutt's System of Medicine," vol. iv, p. 350, gives references to 150 articles published prior to 1897.

forming a pedicle composed of the blood-vessels, ureters, nerves, and peritoneum, constituting what is known as a *mesonephron.* In this condition the organ is movable within the abdominal cavity, and is called a **floating kidney.** Both the movable and floating organs not infrequently twist or kink the ureter, giving rise to obstruction and favoring the development of hydronephrosis. Many of the symptoms of floating kidney are due to ureteral obstruction; this feature also explains the occurrence of the so-called urinary crises, in which unusual amounts of urine are voided during exceedingly brief periods. They result from obstruction and accumulation of urine in the renal pelvis, the contents of which are rapidly discharged as soon as the kidney resumes its normal position. Less commonly, torsion gives rise to a temporary obstruction of the blood supply, and, if the obstruction persist, gangrene of the organ sometimes occurs. The kidney may be displaced and caught by the adhesions, or in other ways incarcerated. The ectopic right kidney may drag upon the peritoneum and cause pressure on the bile-ducts or duodenum, thereby inducing gastric and biliary disturbances; jaundice sometimes occurs. Coincident mucous colitis and appendicitis have been observed. Allglave[1] discusses in detail the possible altered relations of the colon produced by movable kidney. Cabot reports a case of hematuria due to movable kidney, and Sutherland[2] found the ren mobilis in 37.5 per cent. of 40 cases of orthostatic albuminuria.

Malformations of the Ureter.—Sometimes the ureter is imperforate, or, the reverse, sacculated; occasionally, one kidney may possess several ureters; I have seen three ureters on one side. Hohmeier records an instance where a third ureter opened into the vagina. Robinson[3] has shown that the normal shape of the ureteral lumen varies, and often the pair are unlike.

Malformations of the Bladder,[4] Urethra, etc.—Occasionally, the bladder is bifid; sometimes there is a fissure of the abdominal and vesical walls, giving rise to **exstrophy, fissura,** or **inversio vesicæ;** rarely, the bladder is fissured in its posterior wall, and thereby communicates with the pelvic cavity or with the vagina or rectum. The urethra is sometimes imperforate, or the bladder and bowel may possess a single opening; the bladder may be absent. In a few instances the bladder has been found normally formed, but has protruded through a fissure in the abdominal wall—a condition known as *ectopia vesicæ.* Persistence of the urachus may be manifested by a conic projection upward in the median line, the bladder reaching almost, if not quite, to the umbilicus. In other instances the atrophic allantois may remain as a tube-like extension above the bladder, ending at the umbilicus, or it may be closed at both ends. Later, accumulation of fluid in the tube leads to the formation of a cyst, constituting what is known as a **cyst of the urachus.** The urethra may open on the dorsal aspect or on the inferior surface of the penis, giving rise to **epispadias** and to **hypospadias,** respectively. Hypospadias may be balanic, penile, scrotal, or perineoscrotal; it occurs about once in 375 male infants. Occasionally the

[1] "Revue de Chir.," Dec. 10, 1904, p. 730.
[2] "Amer. Jour. of Med. Sci.," Aug., 1903.
[3] "Med. News." Aug. 8, 1903, p. 247.
[4] Enderlen, "Ueber Blasenektopie," Wiesbaden, 1904.

urethra may possess more than one external orifice; sometimes the meatus is bifid. Occasionally, the urethra has more than one external orifice; in rare instances the urethra opens behind the scrotum, giving rise to **hypospadias perineoscrotalis.**

Diseases of the Kidney-bed.[1]—*Atrophy of the perirenal fat* has been described and it has been suggested that abnormal mobility of the kidney may depend upon this cause. Inflammation around the kidney—**perinephritis**—may be acute or chronic, productive or suppurative. The acute form is practically always attended by the development of pus and the formation of a **perinephric abscess.** Usually it is secondary to suppurative processes within the kidney, but may result from extension from contiguous tissues or infection brought by the blood. Primary perirenal abscess is often due to injury. Sometimes the acute form is protracted and there is notable increase in the fibrous tissue forming the wall, with marked sclerosis of the contiguous fat; this has been called **chronic perinephric abscess.** A similar condition sometimes develops insidiously, and is not infrequently manifested by the occurrence of multiple foci of suppuration embedded in a dense fibrous connective tissue, generated by inflammatory hyperplasia of the contiguous fibrous elements. This form is usually due to chronic suppurations within the kidney, and especially to that form of pyelitis which accompanies calculi. **Sclerosing perinephritis** gives rise to a more or less marked increase in the fibrous tissue around the kidney. The condition may be due to inflammations within the kidney or it may be consecutive to other contiguous irritation. Sometimes the fat around an incarcerated movable kidney manifests the change. The kidney is abnormally firmly attached, and during removal brings with it a large amount of the adjacent tissue.

Pararenal cysts sometimes occur; when composed of blood, they are called **paranephric hematomata;** if the cysts contain urine, the condition is called **paranephrosis** or **a paranephric urinary cyst.** Both forms of extravasation are usually due to injury which wounds a vessel or ruptures the pelvis of the kidney or the ureter; lacerations of the kidney substance may also give rise to hemorrhage. In the **urosanguineous cysts** both urine and blood are present. Urine or blood in the paranephric tissues favors the occurrence of infection and consequent suppuration, and may terminate in perinephric abscess.

Diseases of the Kidney.—For pathologic study of the urinary organs it is advantageous to assume that only a part of these structures has anything to do with the secretion of urine. The secreting structure is, of course, the kidney, and particularly that part of the organ lying superficially, and known as the cortex. A study of the relation of diseases of the kidney to the different parts of the organ will show that a number of conditions begin in, and are largely restricted to, the essen-

[1] Saritcheff, "Med. Obosrenie," vol. lvii, No. 3. Verstraete, "Jour. des Sciences méd. de Lille," June 1, 8, and 15, 1901. Edlefesen, "Münch. med. Woch.," Feb. 4, 1902. Waldvogel, "Deut. Zeit. f. Chir.," June, 1902. Newman, "Brit. Med. Jour.," July 19, 1902, p. 167. Schmidt, "Münch. med. Woch.," April 28, 1903, p. 731. Kelley, "Jour. Amer. Med. Assoc.," June 27, 1903, p. 1775. Delbet, "Rev. de Chir.," July, 1903, p. 62. Galladauet, "Annals of Surgery," April, 1904, p. 573. Watson, "Boston Med. and Surg. Jour.," vol. cxlix, No. 2, p. 29, and No. 3, p. 64. Townsend, "Jour. Amer. Med. Assoc.," Nov. 26, 1904, p. 1626.

tial secreting tissue. To this group belong the various forms of Bright's disease and the acute degenerative processes, and constitute what are often called the *medical diseases of the kidney.* In another class of cases the lesions originate in the pelvis, ureter, or bladder, and extend by continuity along the course of the passage, eventually involving, in many cases, the secreting structure of the kidney. With this group of diseases are included certain retention cysts of the kidney (hydronephrosis, pyonephrosis), suppurative lesions, and secondary suppurative processes in the urethra, prostate, bladder, ureter, and pelvis. By common consent these affections are grouped under the term *surgical diseases of the urinary apparatus.* It will be observed that this division into the medical and surgical diseases is largely clinical, but has some foundation in that the morbid conditions which eventually manifest themselves are, to a certain extent at least, largely restricted to the structures just indicated

Atrophy of the Kidney.—Aside from the arrest in development already referred to when considering malformation (and hypoplasia is really not an atrophy), but little is known of atrophic processes in the kidney. The small or contracted kidney resulting from chronic interstitial inflammation is sometimes referred to as an atrophied organ.

Hypertrophy of the kidney occurs to a limited extent in both organs in individuals addicted to drinking large quantities of fluid, and in whom the kidneys are thereby called upon for unusual activity. As a result of disease, of failure of development, or of removal of one organ, its fellow commonly manifests more or less hypertrophy. The earlier in life the functional loss of one organ occurs, the more prompt, and, as a rule, the more complete, will be the compensatory hypertrophy of the remaining kidney. The power, however, of continued enlargement persists until late in life. During the fetal period destruction of one organ leads to enlargement of the remaining kidney until it approximates in volume two fully developed organs. At this time new tubules and new Malpighian tufts may be formed, but later in life, after the kidney has attained its normal dimensions, it is probable that increase in volume is the result of a proportional increase in the size of the tubules, and is unassociated with the formation of new tubules or additional tufts.

Infiltrations of the Kidney.—Fatty and calcareous infiltrations are rare in the normal organ. Calcification is not infrequent in areas of past necrosis, such as those resulting from tuberculosis, infarction, etc. Occasionally, the kidney shows pigmentation resulting from a deposit of more or less altered hemoglobin. The color of the affected area or of the whole organ is brown, brownish-yellow, or mottled. Pigments so deposited may be rich in iron, as can be readily shown by the application of the usual tests. (See p. 236.) In jaundice more or less staining of the kidney tissue is always evident, and usually necrotic and desquamative changes give rise to casts that are intensely bile stained. Aside from the concretions or true calculi occurring in the conducting portion of the urinary tract,—the pelvis, ureter, bladder, and urethra,—there is occasionally observed, in the kidney structure proper, within the tubules, and massed with more or less necrotic epithelium, deposits of uric acid and urates. The so-called **uratic infarcts,** which develop during the first two weeks of postnatal life, are also examples of depo-

sition similar to that just described and occurring in the tubules of the pyramids. In diabetes a varying amount of glycogenic infiltration may be present in the renal epithelium, and, to a limited extent, in the Malpighian bodies. Lardaceous disease of the kidney will be considered with the renal inflammations.

FIG. 315.—KIDNEY, SHOWING GRANULAR AND FATTY DEGENERATIONS OF THE CORTEX, FROM A CASE OF PERNICIOUS ANEMIA.

Osmic acid preparation. Parts of three convoluted tubes and one collecting tube are shown. The epithelium of the two collecting tubes near the center of the drawing is the seat of advanced granular and fatty change. The protoplasm is granular and fragmenting, and contains droplets of fat that have been blackened by the osmic acid.

Degenerations of the Kidney.[1]—True fatty degeneration of the organ can probably be best considered with chronic parenchymatous nephritis, with which it is so constantly associated. A similar conversion of the renal epithelium into fat occurs in pernicious anemia. Parenchymatous degeneration (cloudy swelling) is probably the most constant morbid condition to be recognized in the kidney. It may result from hyperemia, from congestion, or from the presence of various irritants, particularly those elaborated during the progress of infectious diseases, such as scarlet fever, diphtheria, pneumonia, erysipelas, etc. (See causes of acute Bright's disease, p. 641.)

Anatomically, the appearance of the organ is largely dependent upon the amount of vascular distention with which the lesion is associated. In the absence of hyperemia or congestion, the kidney is pale, soft, and not infrequently pits, as though it were edematous. The swelling is often inconspicuous, but can usually be shown to be present by the fact that, upon incision, the capsule retracts. In the absence of congestion or hyperemia the pale, cloudy surface contrasts strongly with the bright luster of the normal kidney. The histologic changes are those already described when considering cloudy swelling. (See p. 241.)

FIG. 316.—CLOUDY SWELLING OF THE EPITHELIUM LINING A KIDNEY TUBULE.—(*Fütterer.*)

Hyperemia of the kidney is induced by exposure to cold, by the administration of irritant substances normally excreted through the kidney, and it also occurs in some, but not in all, febrile conditions, and is present in the initial stage of acute nephritis. (See causes of acute Bright's disease.)

[1] Landsteiner, "Wien. klin. Woch.," Oct. 10, 1901. "Il Policlinico," Nov., 1902. Natason, "Wien. klin. Woch.," July 16, 1903, p. 857. Landsteiner and Mucha, "Centralbl. f. allg. Path. u. path. Anat.," Sept. 30, 1904, p. 752.

Morbid Anatomy.—The organ is somewhat larger than normal, soft, and, on section, drips blood. The cortex is very much darker than that of the normal organ, and is striated, while the medullary portion may be almost purplish. Microscopic examination usually shows distention of the entire vascular area, and, at points, rhexis; cloudy swelling is extremely likely to accompany the condition.

Congestion of the kidney arises as the result of impeded venous circulation, such as may occur in chronic heart or lung diseases, or, locally, from pressure on the renal veins by abdominal tumors, ascites, and a very much enlarged pregnant uterus. The most advanced form of congested kidney is the so-called **cyanotic kidney** of chronic heart disease. (See p. 519.)

Morbid Anatomy.—The organ is usually large and swollen, and may drip blood on section. The tissue is firmer than normal, and resists cutting and tearing, owing to the increase in connective tissue. Unlike typic interstitial nephritis, the capsule usually strips more easily than normal; the cortex is of a deep-red color and often striated, and the pyramids are purplish. Microscopically, the epithelium is cloudy or granular, and at points almost fatty; there is some increase in interstitial supporting structure, manifested by a small lymphoid cell accumulation between the tubes, and also an increase in the fibrous tissue—an evidence of past exudation. The amount of fibrous tissue may be sufficient to lead to a slight reduction in the size of the organ, when the kidney is perceptibly smaller than normal, it is reasonable to assume that an associated chronic interstitial inflammation is present. The blood-vessels are intensely engorged, but rhexis is less commonly present than in the condition of acute hyperemia.

Renal infarction[1] results from embolic or thrombotic occlusion of the renal artery or its branches. The infarcts may be multiple or single and often are of different ages; they are usually anemic. The base presenting on the surface of the organ is round, oval or slightly irregular, pale or nearly white, and often marginated by a hyperemic zone 1 mm. to 2 mm. in breadth. On account of the capsular tension they are rarely elevated to any perceptible degree; the capsule is usually loosely attached to the base of the infarct. Infarcts in the medulla (Fig. 317) are less frequent. The affected kidney is commonly swollen and often pits on pressure. When incised, the wedge-shaped infarct commonly extends to the corticomedullary junction, rarely deeper. When the infarction is due to fat-embolism, oil-droplets are sometimes present in the urine. Hemorrhagic infarcts of the kidney are much less common, and when present possess the usual character of such structures.[2] In exceptional cases the entire kidney is affected; in such instances the process is usually anemic. Weigall[3] reports an instance of gangrene in a movable kidney due to twist in the pedicle.

Hematuria, or blood in the urine, may result from hemorrhage arising in the renal parenchyma or from any part of the conducting path. **Renal hematuria** may attend hyperemia, congestion, infarction, and injuries to the kidney substance, and is present in some forms

[1] Fischler, "Virchow's Arch.," 1902, Bd. 170, p. 1. Schmidt, "Wien. klin. Woch.," May 16, 1901.
[2] See Embolism and Infarction, pp. 278 to 284.
[3] "Australasian Med. Gazette," 1903, vol. xxii, p. 515.

of nephritis, particularly the acute. It is especially marked in the so-called hemorrhagic nephritis, but is infrequent in the chronic inflammations of the organ. It is not certain whether or not the hematuria accompanying purpura and hemorrhagic septicemias is always renal; the occasional presence of blood-casts clearly indicates that the bleeding came from the kidney, at least in some cases. Bleeding from the kidney substance also occurs when primary or secondary tumors involve the parenchyma of the organ. Usually the hemorrhage accompanying renal neoplasms is the result of involvement of the pelvis of the kidney, but not always so, as I have on two occasions observed hematuria with blood-casts and at the autopsy found no structural lesion of the

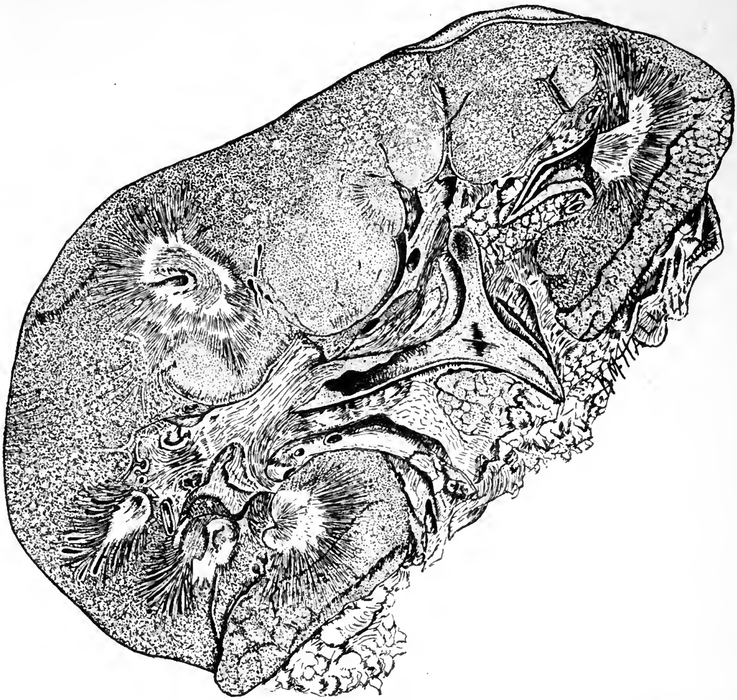


FIG. 317.—KIDNEY, MULTIPLE ANEMIC INFARCTS. CASE OF ULCERATIVE ENDOCARDITIS.

pelvis. Hematuria from a healthy kidney, also called **renal hemophilia,**[1] has been described. Hemorrhage from the conducting portions of the urinary organs may be due to trauma, calculi, ruptured varicose vessels, certain diseases of the prostate, and tumors. Among the neoplasms, papilloma and cancer are the most frequent causes. **Parasitic hematuria** is due to the Bilharzia hæmatobia, and occurs in venal distomatosis[2]; hydatid disease of the kidney may be attended by hemorrhage.

[1] See Douglas, "Surgical Diseases of the Abdomen," 1903, p. 571. Leube, "Deut. med. Woch.," 1905, xxxi, No. 3. Schenck, "Med. News," Dec. 24, 1904, p. 1206.

[2] See p. 193.

When the blood comes from the kidney, it is uniformly distributed in the urine, which is rendered smoky by conversion of the hemoglobin into acid-hematin and methemoglobin. Blood casts and other evidences of renal involvement are usually present.

The term **albuminuria** is applied to that condition in which serum-albumin or globulin, or both, occur in the urine. Two forms are recognized—physiologic and pathologic. In health, by delicate tests, a trace of albumin may be demonstrated in the urine, particularly after exertion and the ingestion of highly albuminous food. The albuminuria following cold baths, and particularly ocean bathing, is usually classed with the physiologic type. The so-called physiologic or functional albuminuria is practically always of brief duration, or at least intermittent. Personally I am inclined to agree with the insurance companies which decline to accept the excretion of albumin as a normal process. **Incidental albuminuria** results from the addition of albumin to the urine as a result of diseases affecting the conducting passages, and arises from essentially the same causes as the analogous type of hematuria, which has already been discussed.

Pathologic albuminuria of renal origin may be accepted as always indicating some structural alteration in the kidney. It accompanies hyperemia and congestion, is very frequently associated with febrile processes and toxic conditions, and is almost constantly present in inflammation of the kidney. A number of observers, and more recently Cabot,[1] have shown that nephritis may occur without albuminuria, and that often the amount of albumin in the urine bears no relation to the intensity of the renal inflammation. With regard to the exact nature of albuminuria we are indifferently informed. Authorities are not agreed as to whether it is a transudate, an exudate, or a secretory product of the altered renal tissue. The fact that foreign albumins thrown into the blood quickly appear in the urine indicates that the epithelial cells are able to secrete this form of proteid matter; that they do so in disease is not established. The occurrence of albuminuria in connection with the heightened tension of renal congestion and hyperemia suggests transudation, and the frequent abundance of albumin in the urine from kidneys in which admittedly exudative inflammations are in progress may be taken as establishing its production by exudation. The three illustrations just mentioned, and others that might be given, clearly indicate that the albumin does not always result from the same primitive change in the kidney.

Renal casts[2] are cylindric bodies formed in the uriniferous tubules, from which they are discharged into the urine. Of the many suggested methods by which they are produced, three are deserving of mention. Rovida believed they were derived from epithelial cells, and, in a sense, were secretory products. Key and also Bayer conceded the epithelial origin of these bodies, but thought they resulted from destructive metamorphosis of the renal epithelium. Following Traube, many have contended that they are solidified exudates and

[1] "Jour. of Amer. Med. Assoc.," March 18, 1905. See also Köresi, "Wien. klin. Woch.," Oct. 13, 1904, p. 1075. Orgler, "Virchow's Arch.," 1904, Bd. 176, p. 413.

[2] The literature of the subject may be followed from Coplin, "Phila. Med. Jour.," March 8, 1902.

always due to inflammation. The theory that they are composed of albumin, solidified in the tubules by the action of urine, is suggestive of their exudative origin. Microchemically it is possible to demonstrate that some of the casts contain mucin, others give the reaction for fibrin, and many contain fat. These facts, however, do not elucidate their origin; it is probable that they arise in more than one of the ways suggested, and that under different conditions the process by which they are formed is not always the same. Casts containing blood are called **blood casts.** When the epithelial cells, adhering to, or forming part of, the structure, can be identified, they are known as **epithelial casts.** The **granular cast** probably results from degeneration of epithelial cells and other structures, possibly leukocytes, attached to or forming part of the cast. In a similar way fatty change gives rise to **fatty casts.** Large, rigid, highly refractile cylinders of this type are called **waxy casts.** **Hyaline casts** are usually smaller, structureless, and difficult to recognize. It is not improbable that the body or core of other forms of casts is composed of a substance resembling, or identical with, that found in the hyaline cast. Casts composed of leukocytes, and others containing numerous bacteria, occasionally are found in the urine.[1] It is well known that on standing casts may disappear from the urine, and that they are most abundant in specimens freshly voided. In the presence of pus they rapidly disintegrate, and the larger the number of bacteria, the more rapid the disintegration. Treutlein[2] has shown that some bacteria are more active than others in the destruction of casts. He calls the process **cylindrolysis.**

Nephritis or **inflammation of the kidney** includes a number of the most important diseases, and at the same time, because of its varied manifestations, offers the greatest difficulty in the systematic grouping of the various forms. In the present state of our knowledge it is impossible to say exactly what changes in the kidney are inflammatory and thereby draw a sharp line between nephritis and the degenerations and necroses that affect the organ. Clinically, it is possible to recognize acute and chronic forms, and usually the anatomic changes enable us to differentiate the organs resulting from recent active inflammatory processes, from those in which the affection is of longer duration. In some inflammations of the kidney inflammatory exudates are formed within the tubules or in the interstitial structure, and to such processes the name **exudative nephritis** has been applied. In other cases, often without marked alteration in the epithelium of the organ, particularly in the earlier stages, there is a notable increase in the fibrous tissue between the tubules, justifying the term **productive nephritis.** In still another group of cases exudation is absent or but slight, and retrograde changes in the epithelium conspicuous; these have been called **degenerative inflammations.** Occasionally exudative, productive, and degenerative lesions affect the same organ, giving rise to an extremely confusing anatomic picture that does not adapt itself to any one of the previously mentioned groups. As is well known, the kidney, like other glandular viscera, is composed of a connective-tissue framework in which are distributed the blood-vessels, lymphatics, and nerves; this structure is called the interstitial

[1] For methods of demonstration and illustrations showing different forms of casts see chapter on Examination of the Urine at the end of this volume.

[2] "Münch. med. Woch.," 1903, No. 35.

tissue. The part of the kidney which accomplishes secretion is the epithelium lining the tubules and the Malpighian tufts; this constitutes the parenchyma of the organ. The recognition of the two types of tissue led to the classification of renal inflammations based upon this fact. **Interstitial nephritis** was supposed to have its origin, and to induce its conspicuous changes, in the interstitial tissue. **Parenchymatous nephritis,** on the other hand, was presumed to arise in, and to be largely restricted to, the epithelium of the tubules, and hence by some writers it is called catarrhal nephritis. It was soon recognized that, neither clinically nor anatomically, is it possible to establish a form of renal inflammation affecting either the interstitial tissue or the tubular tissue exclusively. The recognition of this fact led to a further group in which both the interstitial and the parenchymatous structures were involved, and to which the name **diffuse nephritis** has been given.

All attempts to bring order out of this chaos have been unproductive of satisfactory results. No classification of renal inflammations has met the approval of both clinicians and pathologists. The extremely complex groupings, rendered possible by an accurate knowledge of the morbid anatomy, do not yield themselves to the clinical picture encountered in the sick. For this reason I shall adopt a classification of renal lesions into forms that can be recognized clinically, and will at the same time point out the anatomic differences upon which more detailed subdivisions may be made. I shall consider—(1) the acute suppurative interstitial nephritis. (2) Acute Bright's disease or acute diffuse nephritis, with which I shall include the acute nonsuppurative interstitial nephritis and the acute parenchymatous nephritis. (3) Chronic diffuse nephritis, embracing both the large white and the small white kidney, is also called chronic parenchymatous nephritis. (4) Chronic interstitial nephritis. This classification[1] must be regarded as provisional, adapting itself to the recognized clinical forms of nephritis and offering an acceptable basis for appropriate description of the lesions observed.

Acute suppurative nephritis is an inflammation of the kidney attended by the production of an exudate in which polymorphonuclear leukocytes predominate. Primarily the process is intertubular, and might with propriety be called **acute suppurative interstitial nephritis.** In some cases definite abscess formation results, while in others the suppuration seems more diffuse. Necessarily the process is due to infection by pyogenic bacteria. These organisms may reach the kidney by extension from the pelvis (**pyelonephritis**), by invasion from the perinephric tissues, and by the blood; the last is the usual path. The bacteria commonly present are streptococci, pneumococci, staphylococci, the Bacillus coli, and the typhoid bacillus. Something in the virulence of the organism, in the susceptibility of the patient, or something in the associated intoxication, seems necessary to produce definite colonization from hematogenous infection. It is well known that in typhoid and pneumonia the specific organism is commonly present in

[1] Those desiring to familiarize themselves with other classifications should consult Councilman, "Med. and Surg. Reports of the Boston City Hospital," eighth series, 1897, p. 31. Bradford, "Lancet," July 4, 1903, p. 1, July 16, 1904, p. 125, and July 23, 1904, p. 191. Tyson, "Bright's Disease and Diabetes," 1904, pp. 83 to 99. Herrick, "Med. Rec.," June 14, 1902.

the blood, and still acute suppurative nephritis may be regarded as an infrequent complication of these conditions, while the nonsuppurative form of interstitial nephritis occurs much more commonly. It may be that congenital peculiarity[1] determines unusual susceptibility, but probably the question of intensity of infection and lessened resistance on the part of the tissues are the important factors. A true suppurative nephritis occasionally accompanies diphtheria and scarlet fever, in which conditions it often appears to be superadded to the acute parenchymatous or acute nonsuppurative lesion. In pyemia and septicemia, and in processes associated with the presence of infected emboli, an acute suppurative nephritis progressing to abscess formation is not infrequently present.

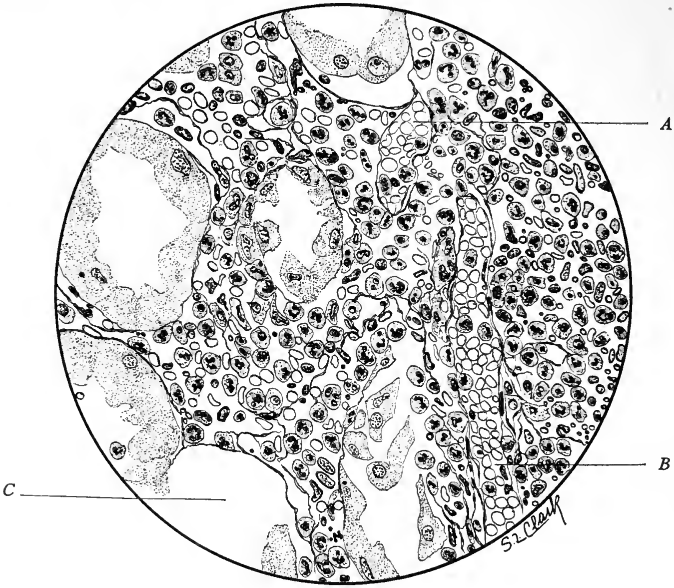


FIG. 318.—KIDNEY, ACUTE SUPPURATIVE INTERSTITIAL NEPHRITIS.

A and *B*. Distended blood-vessels; the numerous leukocytes mixed with the erythrocytes are almost exclusively of the polymorphonuclear type, and the same cells form the major portion of the intertubular exudate, although a few red cells have also escaped. The swelling is indicated by the dissociation of the interstitial tissue. The variation in size manifested by the red cells is the result of sectioning, many of them having been divided by the knife. *C*. Tubule which has shed most of its epithelium; the remaining cells in this tubule and those present in other tubules are advancedly granular, evidently necrotic.

Morbid Anatomy.—In the absence of recognizable abscesses the macroscopic differentiation of this condition is often most difficult and sometimes impossible. The organ is usually enlarged—sometimes the swelling is extremely marked; the capsule is tense, and occasionally grayish miliary abscesses may be recognized in subcapsular tissues. When incised, the capsule retracts and the cortex bulges; the resistance to incision is not increased. The appearance of the cut surface is rarely the same in any two cases. In some instances it is pale, in others hyperemic, and may drip blood, particularly if the condition be asso-

[1] For suggestive paper dealing with the susceptibilities to nephritis see Castaigne and Rathery, "La Sem. Méd.," 1903, p. 309.

ciated with an acute diffuse lesion. Where the infection has extended from the pelvis (**pyelonephritis**), the lines of suppuration may often be traced in the pyramids and extending upward into the cortex; they consist of grayish, white, or whitish-yellow striæ radiating from the apex of the pyramid. When miliary abscesses are present, the incised surface is dotted with yellowish or yellowish-white bodies 1 mm. to 2 mm. in diameter; in some points these may have become confluent, producing abscesses of larger size. The embolic abscesses may be distinctly conical or confluence may give rise to irregular areas of suppuration. In hematogenous infection, unattended by macroscopic evidences of embolism, suppuration is frequently conspicuous in the areas of the labyrinth, some of which may be outlined with remarkable clearness. In some instances of infection from the blood striæ in the pyramids result from interstitial suppuration between the straight tubules, which may also be due to extension from the tubules, carrying bacteria derived from centers of infection in the areas of the labyrinth.

The histology of the affection is almost as varied as the gross anatomy, but the affection is constantly differentiated from other forms of nephritis by the enormous numbers of polymorphonuclear leukocytes observed in the lesion. Other white blood-cells may be present, but, when compared with the predominant pus-cell, are never numerous. The enlargement of the organ is due to a marked intertubular swelling and cell accumulation. Necessarily the parenchyma suffers in direct proportion to the intensity of the process. In the beginning of the lesion, or toward the margin of defined abscesses, the tubular epithelium is found necrotic, granular, and desquamating; often distinct casts composed of the necrotic cells are observed within the tubes; many of the affected tubules contain cylinders in which the number of polymorphonuclear leukocytes is sufficient to justify the name pus casts. In the Malpighian tufts definite emboli may be recognized, and sometimes hyaline thrombi are present; there is practically always a cellular exudate into the cavity of the tuft, and within this numerous polymorphonuclear leukocytes are frequently found. Throughout the lesions the causative bacteria are present in varying numbers; in some cases bacterial plugs, or definite colonies, may be recognized in the capillaries, especially of the tuft; in other cases the number of bacteria is small and the organisms proportionately difficult to find. It is well known that the acute diffuse and acute nonsuppurative interstitial nephritis may involve kidneys which, by all the methods at our disposal, appear sterile. I do not believe that acute suppurative nephritis ever occurs in the absence of bacteria within the lesion. Occasionally a large amount of blood will be found diffused through such kidneys, thereby constituting a form of hemorrhagic nephritis; such cases are rare.

Under the term **acute Bright's disease**[1] or **acute diffuse nephritis**

[1] See references to Councilman, and Bradford, foot-note on p. 641. Also Councilman, "Trans. Assoc. Amer. Phys.," 1898, vol. xiii. Baginsky, "Arch. f. Kinderheilk.," xxxiii, Nos. 1 and 2. Howard, "Amer. Jour. of Med. Sci.," Feb., 1901. Raymond and Hulot, "Soc. de Biol.," Dec. 21, 1901. Miller, "Arch. of Pediatrics," Jan., 1902. Welch and Schamberg, "Phila. Med. Jour.," Nov. 1, 1902, p. 637. Mensi, "Gazetta Medicina Italiana," 1903, 21, p. 207. Swan, "Amer. Jour. of Med. Sci.," 1904. Lyon, "Jour. of Path. and Bact.," July, 1904, p. 400. Fichera and Scaffidi, "Virchow's Arch.," 1904, vol. 177, p. 63. Flamini, "Il Policlin.," Sept., 1904. Sollmann, "Jour. Amer. Med. Assoc.," Nov. 26, 1904, p. 22. Reichel, "Zeit. f. Heilk.," 1905, Bd. xxvi, H. 1.

I shall include the renal inflammations to which the names *acute parenchymatous nephritis*, *acute degenerative nephritis*, *acute tubular nephritis*, *acute catarrhal nephritis*, *fibrinous nephritis*, and *acute desquamative nephritis*, have been applied. I shall also place with this group the anatomic form which justifies the name *acute nonsuppurative interstitial nephritis*. Councilman is clearly correct in maintaining a distinct anatomic position for this type of renal inflammation, but I am advised by clinicians (Tyson takes this view) that it offers no symptomatic phenomena by which it can be distinguished from closely allied conditions.

Acute nephritis is a manifestation of renal irritation, and the irritants that may give rise to the condition are many and varied. Of the large number of medicaments enumerated by Sollmann as capable of producing nephritis, turpentine, cantharides, potassium chlorate, carbolic acid, less commonly cubebs and copaiba, and certain metals, among which should be mentioned arsenic, mercury, phosphorus, and the salts of chromium, are especially important. The influence of cold and exposure has been variously estimated; the statement that "a man gets drunk, sleeps in a ditch, and passes bloody urine the next morning" has been very generally accepted as epitomizing a clinical observation. Such influences probably act by suppressing cutaneous secretion and proportionately increasing the quantity, and possibly altering the character, of the irritants which the kidney must excrete. This necessarily enhances the renal irritation and, if not actually productive of inflammation, must increase tissue susceptibility to other factors giving rise to acute nephritis. An acute inflammation of this type sometimes accompanies gestation, in which condition it is probably a part of the toxemia of pregnancy to which I have referred on page 80. Clinically nephritis of the acute type is so frequently associated with certain infectious diseases, especially scarlet fever and diphtheria, that it is sometimes referred to as **postdiphtherial** or **postscarlatinal nephritis.** Acute renal inflammation is a frequent manifestation in puerperal and other forms of sepsis, which, with propriety, may be considered with the infectious diseases. Miller has been able to collect forty cases of influenzal nephritis in which the renal manifestation sometimes assumes a hemorrhagic type. Welch and Schamberg found albumin in sixty-five per cent. of the cases of smallpox, and in forty-five per cent. casts were also present. As a rule, **variolous nephritis** is less intense than that occurring in scarlet fever. Pneumonia, both croupous and bronchial, more commonly the former, may also give rise to the condition. The nephritis accompanying erysipelas may be of this type or it may be acute suppurative, and in some cases both lesions are concurrent. Acute nephritis may be produced by the injection of bacterial toxins, especially the poisons derived from the diphtheria bacillus, and in the infectious diseases, with which it occurs, it seems reasonably evident that the renal disturbance is due to the action of toxic substances reaching the kidney by the blood. The nephritis occasionally accompanying syphilis[1] may be of this type. It is sometimes

[1] See Hoffman, "Berl. klin. Woch.," March 3, 1902. Waldvogel, "Deut. med. Woch.," Oct. 30, 1902. Wagner, "Münch. med. Woch.," Dec. 16, and Dec. 23, 1902, p. 2150. Mühlig, "Münch. med. Woch.," March 24, 1903, p. 505. Carpenter, "Lancet," Aug. 15, 1903, p. 473. Sutherland and Walker, "Brit. Med. Jour.," April 25, 1903, p. 959. Schlechtendahl, "Wien. klin. Rundschau," Aug. 16, 1903. Thiemann, "Münch. med. Woch.," Jan. 31, 1905.

difficult to say whether the inflammation is due to the syphilis or to the mercury used in treatment; as some cases recover during the continuous administration of the remedy, it is evident that the latter is not the cause in all instances. It is to be remembered that syphilis may also induce chronic forms of nephritis. The acute inflammation accompanying syphilis is frequently hemorrhagic, and the amount of albumin present is sometimes enormous; in the case reported by Hoffman, the urine contained eight per cent. (by weight) of albumin.

The foregoing summary of the conditions under which acute nephritis may occur clearly indicates that we can not look upon the disease as etiologically specific. It is a result of the action of irritants upon the kidney, and as these substances differ in kind, and in intensity of action, the varied morbid anatomy, and somewhat inconstant symptomatology, could, with safety, be predicted. Vaughan proposes to call the poisons producing necrosis and inflammation of the kidney **nephrolysins**; unfortunately, the term has been used with a slightly different meaning and can not be applied without danger of confusion. Lindemann, by subjecting guinea-pigs to hypodermic injections of emulsions prepared from the kidneys of rabbits, obtained, from the treated animals, a nephrolytic serum[1] capable of producing albuminuria and renal inflammation when injected into dogs.

Morbid Anatomy.—Both kidneys are affected, but often to different degrees. The appearances observed postmortem are modified by the duration and intensity of the process, the presence or absence of complications, and also the previous condition of the affected organ. In the earlier stages the kidney may show no conspicuous alteration, or at least nothing indicative of this form of nephritis; usually such organs are intensely hyperemic and mottled, but they may be pale. When the condition is fully developed, the kidney is swollen, often conspicuously enlarged, the capsule tense and immediately retracting on incision. It is less firmly attached than normal and strips off readily. In the presence of marked edema the capsular adhesion is very much less firm than in normal kidneys. The resistance to incision is less than in health and the incised surface bulges. The evident increased tension is often made apparent by the bulging which follows a slight cut through the capsule of a previously unopened organ, and it is possible that the pallor sometimes seen is partly due to the blood being expressed by the recoil of the extremely tense capsule. In the presence of marked hyperemia and associated edema, the incised surface may drip blood or bloody serum. Closer inspection shows that the swelling is most conspicuous in the cortex, which is usually greatly broadened. When the hyperemia is not intense, the areas of the labyrinth are redder than the adjacent cortical pyramids or the medulla; this gives rise to cortical striation, which in some cases is conspicuous. Punctate hemorrhages are sometimes present. As the disease progresses the intense hyperemia gradually lessens and the organ becomes paler. In the later stages it is often possible to detect cortical striation due to the necrotic and degenerative changes in the areas of the labyrinth. When such retrograde alterations are marked, the areas containing the

[1] Schültze, "Deut. med. Woch.," 1900, No. 27. Ascoli and Figari, "Berl. klin. Woch.," June 16, 1902. Pearce, "Jour. of Med. Research," 1904, vol. xii, p. 1.

convoluted tubules are extremely pale. The decapsulated and incised surfaces of the organ are often mottled, due to different degrees of hyperemia, and areas of necrosis and degeneration irregularly distributed in the superficial cortex and within the organ. Often the Malpighian bodies can not be recognized; in other cases they are pale and bloodless, but when involved in the inflammatory process they appear dark and intensely hyperemic in the earlier stages and later become pale from the presence of the exudate and associated necrosis and degeneration. The pelvis of the kidney is occasionally the seat of well-marked inflammation; the mucosa may be red and injected and manifest the usual evidences of an acute catarrhal inflammation. In rare cases a distinct pseudomembrane is present. Hemorrhages in the renal bed are infrequent, and when present are usually petechial or ecchymotic. (See Plate XVII, Figs. 2 and 4.)

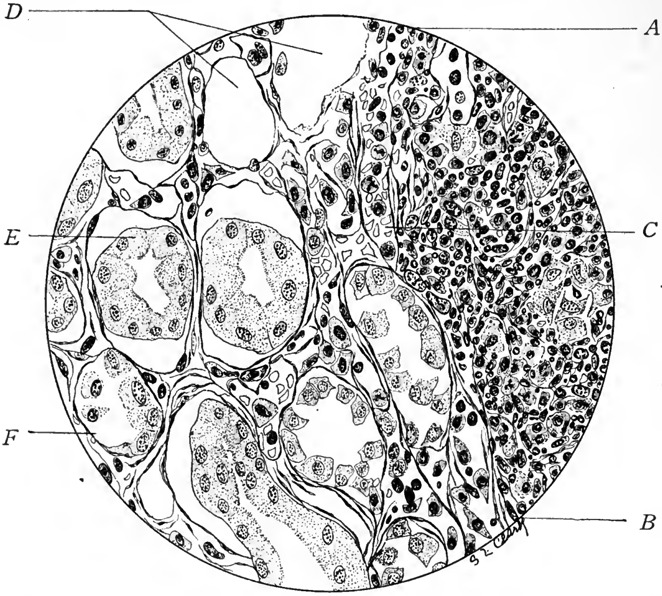


FIG. 319.—KIDNEY, ACUTE, NONSUPPURATIVE, INTERSTITIAL NEPHRITIS. (Compare with Fig. 318.) *A* to *B*. Between the leaders from these points the renal architecture has been largely destroyed and replaced by leukocytes, almost exclusively of the mononuclear type. *C*. Small vessel containing fragmented red blood-cells and an excess of leukocytes, one of which, the second above the leader, is a typical polymorphonuclear white cell. *D*. Two tubules from which the epithelium has been shed. *E* and *F*. Tubules in which epithelial desquamation is progressing; the alteration is more marked in *F*. The artist has brought out the nuclei of epithelial cells with unmerited accentuation, as in this condition they rarely show so clearly.

The histologic changes are also varied. In some cases, and it is probable that this is a beginning inflammation, the interstitial change is slight—scarcely perceptible. The renal epithelium is granular, necrotic, and desquamating; granular casts can be seen in the tubes and sometimes blood casts are present. The epithelium of the Malpighian tufts is also swollen, and there may be some evidence of exfoliation. It will be observed that the brunt of the process falls on the secreting epithelium, and hence justifies the name **acute parenchymatous nephritis.** In another group of cases the changes in the

epithelium are similar to those already described, the hyperemia is much more intense, and cellular exudation is present between the tubules. In some of these cases the intercellular changes are most conspicuous. The migrated cells are mostly mononuclear leukocytes and, as shown by Councilman, Howard, and Lyon, plasma cells[1] are often exceedingly abundant. These latter structures frequently contain mitotic figures. In the absence of frank infection polymorphonuclear leukocytes are not numerous. In these cases the tubular change may be slight; the most conspicuous alteration is exudation in the intertubular structures, and for this reason the condition has been called **acute nonsuppurative interstitial nephritis.** It must not be gathered, however, that the parenchyma escapes; the parenchymatous changes are always present and sometimes marked, and in this sense the lesion is an **acute diffuse nephritis,** involving both the interstitial and the tubular tissues. Casts are numerous within the tubules, and may be granular, epithelial, leukocytic, or contain red blood-cells. The glomerular changes in the different forms of diffuse nephritis vary. In the acute, nonsuppurative interstitial nephritis the capillaries of the tufts contain but few or no red cells. Hyaline thrombi are sometimes present and fibrin may be demonstrated within and around the tuft and sometimes in the interstitial tissue. In **glomerular nephritis** the tuft changes are most conspicuous. Mononuclear cells, many of which are the plasma cell type, form mantles around the tuft; the epithelium is desquamating, and a hyaline or granular deposit fills the space between the mass of convoluted capillaries and the capsule of Bowman. The desquamated epithelium is granular and late in the affection may be shown to contain fat. Those cases of nephritis in which epithelial desquamation is marked, often leaving many tubules stripped of their lining cells, have been called instances of **acute desquamating nephritis** or **acute catarrhal nephritis.**

Bacteria are frequently absent in this form of renal inflammation, and it has been clearly established that they are in no way necessary for its production. Streptococci, pneumococci, staphylococci, the diphtheria bacillus, typhoid bacillus, colon bacillus, influenza bacillus, gonococcus, and occasionally other organisms are found, but even in organs containing bacteria the number is rarely large. Concerning the changes that result in nonfatal cases we possess but little accurate information. Baginsky and others believe that they have been able to trace cases of chronic nephritis to an acute diffuse lesion of the type now under consideration. Certainly if intertubular changes have occurred,—and they are present in most cases,—the kidney must be left correspondingly damaged; the extent of the injury, however, must vary widely, and no doubt the recuperative power of many individuals, especially children, in whom the disease is frequent, is able to establish a physiologic if not structural normal. In no other way can we account for the well-established clinical fact that many children pass through an attack of postscarlatinal nephritis and never afterward manifest any symptoms indicative of renal lesion. Others are less fortunate the affection terminating in a subacute or chronic diffuse nephritis from which recovery rarely ensues.

Among the important lesions accompanying acute nephritis special

[1] These bodies are described on p. 303.

mention should be made of dropsy and anemia, both of which are extreme. The dropsy involves the subcutaneous tissues and may be universal; large fluid accumulations frequently form in the serous cavities; laryngeal edema is sometimes observed. These patients occasionally develop pericarditis, pleurisy, bronchitis, bronchopneumonia, or even a true croupous pneumonia; it is probable that these have no immediate connection with the renal condition except such influence as is manifested by reduced resistance to infection. Myocardial degenerations, and evidences of cardiac failure, are sometimes observed; occasionally an acute nonsuppurative interstitial myocarditis is present. It is probable that the alterations in the heart muscle are produced by the same causes as produced the nephritis, and are therefore independent; they are no doubt intensified and their influence prolonged by the concurrent renal lesion. The clinical condition called uremia is often present. The anemia of Bright's disease is of the secondary type (see p. 419).

The urinary changes accompanying acute nephritis[1] are not always the same and in some cases are not marked, In the earlier stages the quantity of the urine is diminished and in some cases actual suppression occurs. The urine secreted in small quantities is usually highly colored, of a high specific gravity, and, from the admixture of blood, smoky or darker in hue. In the earlier stage the amount of albumin is usually abundant, and may be so great that when a small test-tube containing the urine is immersed in boiling water, the contents solidify; the quantity of albumin becomes less as the case advances, and later may be absent, although a microscopic examination of the urine continues to show that renal changes are still in progress. In the beginning of the attack the character of the formed elements observed in the urine is determined by the extent of the hyperemia, the abundance of the exudate, and the amount of renal necrosis, degeneration, and desquamation. Casts are usually abundant, and may be composed of epithelium or blood; later the blood casts become less numerous, although epithelial, granular, and fatty casts linger into convalescence. As recovery proceeds the epithelium seen in the casts improves, and eventually disappears; a few hyaline casts continue for a short time, but gradually no more can be found; the albumin slowly diminishes and eventually disappears, the reduction in urea is fully made up, and the kidney resumes its normal functions. When the disease is progressing into the chronic form, the epithelial cells, occurring in the casts, do not return to anything like their normal condition, but remain more or less granular and sometimes fatty; the amount of urine remains diminished, urea excretion does not rise to the normal, and albumin, in a varying quantity, persists.

Chronic diffuse nephritis,[2] also called *chronic parenchymatous nephritis*, *chronic tubular nephritis*, *chronic catarrhal nephritis*, *chronic desquamative nephritis*, *chronic epithelial nephritis*, *chronic renal de-*

[1] For technic see chapter on Examination of the Urine; the varieties of casts are shown in the illustrations accompanying that chapter.

[2] See Bradford, "Lancet," 1901, vol. i, 1903, vol. ii, and 1904, vol. ii. Weber, "Lancet," April 26, 1902. Senator, "Deut. med. Woch.," Jan. 1, 1903. For ocular complications of Bright's disease see Stricker, "Jour. of Amer. Med. Assoc.," Feb. 20, 1904.

generation, and in one form, *large white kidney*, and in another, *small white kidney*, is characterized by degeneration of the renal epithelium and in some cases marked interstitial changes. It is possible that it is sometimes a sequel of the acute diffuse nephritis; commonly, however, it comes on insidiously without any distinctly antecedent inflammatory disturbance. In such cases it has been attributed to overwork of the kidney such as occurs in beer-drinkers and consumers of large quantities of alcohol. It is probably the result of a slowly acting but long-continuing irritation incident to the excretion of some toxic substance. It is probable that different irritants are present in different cases. It is sometimes associated with chronic suppuration and chronic infections, such as tuberculosis and syphilis. The disease occasionally follows acute febrile processes, and it has been observed after prolonged malarial infection. A similar, apparently identical change accompanies amyloid disease of the kidney, and occasionally parenchymatous nephritis terminates in lardaceous disease. Chronic diffuse nephritis is a disease of young adults and occasionally of children.

Morbid Anatomy.—It is customary to recognize two forms of chronic diffuse nephritis; in one of these the organ is large, pale, and anemic, and is called the large white or large fatty kidney; in the other form the organ is small, commonly firm, and is usually anemic; it is known as the small white kidney or pale granular kidney. (See Plate XVII.)

The typical *large white kidney* is of rare occurrence; both kidneys are involved, but not always to the same degree; they are very much enlarged and may weigh twice the normal. Examination of the affected organ shows that it is pale, white or yellowish-white, the capsule is thin and may appear edematous; the stellate veins are rendered more conspicuous by the pallor of the underlying tissues, and they also appear enlarged. Sometimes the organ is edematous and pits on pressure; as a rule, however, this feature is absent. The renal tissue does not resist incision, and the incised surfaces are usually pale and bloodless. In some cases, however, hemorrhages into the kidney occur; this phenomenon has been attributed to fatty degeneration of the capillary walls. The cortex is enormously swollen and may be as broad as the medulla. As soon as incised, the capsule retracts, the cortical portion bulges forward, and the pyramids often appear depressed; usually the pallor of the medullary portion is less evident than that of the cortex, and sometimes the pyramids are distinctly pink. The capsule strips readily and the surface left behind is smooth and slightly mottled. Although great stress is laid upon the size of the organ, it is often but little enlarged, and both kidneys are rarely affected to exactly the same degree, although neither ever escapes.

Histologically the epithelium of the tubules will be found in all stages of desquamation and granular and fatty degeneration. Many of the convoluted tubes contain hyaline, fatty, or granular casts. In others the epithelium is absent. Desquamation and degenerative changes are usually manifest in the epithelium of the tufts. The capillaries in the Malpighian bodies are frequently the seat of hyaline degeneration and occasionally contain hyaline thrombi. The capsule of Bowman is rarely normal, although the increase in connective tissue is usually slight. Sometimes there is marked intertubular swelling, but, as a rule, the interstitial tissue contains but few cells. In some

cases the tendency toward interstitial hemorrhage is quite marked and in such instances numerous erythrocytes may be found between the tubules. The areas of hemorrhage are small, irregularly distributed, and never abundant. I have not been able to satisfy myself that there is fatty degeneration of the capillaries, and think that the hemorrhage is probably due to increased arterial tension without provisional thickening of the capillary wall, the support of which is lessened by the degenerative changes in the renal parenchyma; this type of the affection is sometimes called **chronic hemorrhagic parenchymatous nephritis.**

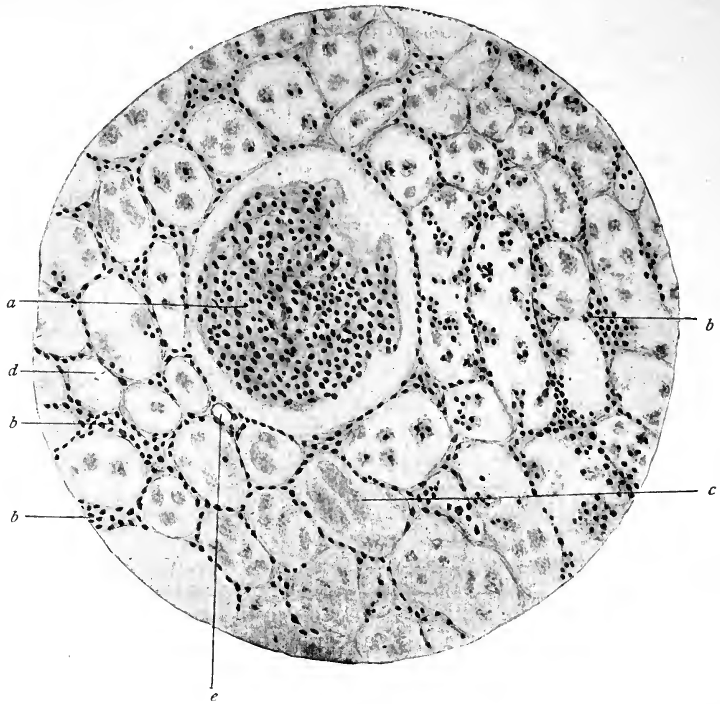


FIG. 320.—CHRONIC PARENCHYMATOUS NEPHRITIS. ($\frac{1}{8}$-inch objective, 1-inch ocular, slightly reduced.) Tissue hardened in corrosive sublimate, infiltrated with paraffin, and stained with hematoxylin and eosin. *a.* Malpighian tuft, containing an unusual number of nuclei. *b*, *b*, *b*. Points at which there is some slight increase in the interstitial tissue. This is not, however, at any point marked. *c*. Tubule containing granular, degenerating, epithelial cells, which have coalesced. In many tubules the fragmented and desquamated epithelial cells in all stages of granular change are to be seen. In no tubule are the epithelial cells normal or normally arranged. *d*. Tubule from which all the epithelium has desquamated and been discharged. *e*. Blood-vessel. (Kidney from a case of tubal nephritis that terminated in death from eclampsia at the end of eleven weeks after the appearance of the first symptoms.)

The fact that the toxic substance to which the disease is due seems to spend its influence on the renal epithelium justifies the names given to indicate this feature, such as parenchymatous, tubal nephritis, etc. There may be some doubt as to whether the change in the epithelium is fatty degeneration or a necrosis. Analysis of a large white kidney usually fails to disclose any conspicuous increase in the fat-content of the organ. There seems to be no doubt that the epithelial cells die in large numbers, although there is less certainty as to the nature of

the process by which they are destroyed. If a thin slab of such a kidney be exposed to the action of osmic acid, the medullary portion is but slightly darkened, the corticomedullary area the least changed, while the labyrinth is rendered absolutely black. Sections of a kidney treated in this manner show the epithelial cells loaded with brownish-black or black bodies indistinguishable from fat. Similar changes can be demonstrated in tube-casts.

The *small white kidney* differs from the preceding in that its surface is granular, its capsule more adherent, its cortex less swollen; indeed, the latter may be thinner than that of the normal organ; the kidney is firm, and cuts with more resistance than the normal. Histologically, the same tubular and tuft changes as those already described in the large white kidney will be found present; there is, however, a notable increase in the connective tissue, more marked in some places than in others; many of the tufts will be found fibroid and atrophied, and many of the tubules compressed or occluded by contraction of the newly developed connective tissue.

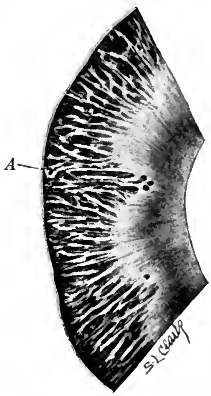


FIG. 321.—KIDNEY, CHRONIC DIFFUSE NEPHRITIS.
One-half normal size. Gross specimen treated with Marchi's fluid. *A*. Fatty areas in the cortex largely restricted to areas of labyrinth.

If one looks merely at the pathologic picture that this type represents, he is led to view the condition as one of chronic tubular inflammation, with superadded interstitial change. As will be seen later, there are many of the elements present that are to be noticed in the chronic interstitial nephritis, and, as already described, many of the changes constantly associated with parenchymatous nephritis, and there is no reason, either etiologic or anatomic, for believing that it is impossible for the two forms of nephritis to intermingle. At present this question can not be definitely settled, so that writers variously classify the small white kidney, some holding that it is produced in a way entirely distinct from the chronic parenchymatous or the chronic interstitial, others maintaining that it is but a form of the chronic parenchymatous or a tubular lesion ingrafted on an interstitial nephritis, or a parenchymatous nephritis that has persisted sufficiently long to develop fibroid changes in the intertubular connective tissue. When the kidney is considered as a mucous membrane, the resemblance between the changes seen in the submucosa after protracted inflammations of the mucous membranes and the interstitial changes observed in the kidney subsequent to a prolonged inflammatory lesion of the tubules become quite evident.

Chronic diffuse nephritis is almost invariably attended by dropsy. The edema may be slight or quite marked. It is usually greater in the typic large white kidney than when the organ is small and fibroid. Uremia is also more common in cases of large white than small white kidney. Retinal lesions are less frequent than in the chronic interstitial nephritis. Hypertrophy of the heart, except in children, is rare, although with beginning contraction the blood-pressure is slightly elevated and the muscle of the heart, particularly of the left ventricle, usually increased. A marked secondary anemia is practically always present.

Changes in the urine accompanying chronic diffuse nephritis: Usually the urine is diminished in quantity, and sometimes the secretion for the twenty-four hours does not exceed 250 c.c. In other cases the daily output approximates the normal, although a careful study commonly demonstrates that the solids fall short. The specific gravity depends more upon the quantity than upon other factors. Usually it is lower than in health. The quantity of albumin varies, but is commonly large; occasionally the urine contains more than the blood. The urea excretion is practically always below the normal, and is less influenced by diet than is the secretion from unaltered kidneys. The other urinary solids are also reduced. The sediment is usually abundant and rich in casts, of which the granular and fatty types indicate the character of the change in the renal epithelium. Hyaline and epithelial casts containing leukocytes, and occasionally blood casts are present; the last-named structures are particularly abundant in hemorrhagic cases. The continued presence of fatty and epithelial casts is the best indication of persisting degenerative changes in the renal epithelium. The urinary changes of the small white kidney are less marked than when the renal lesion manifests no tendency to fibrosis.

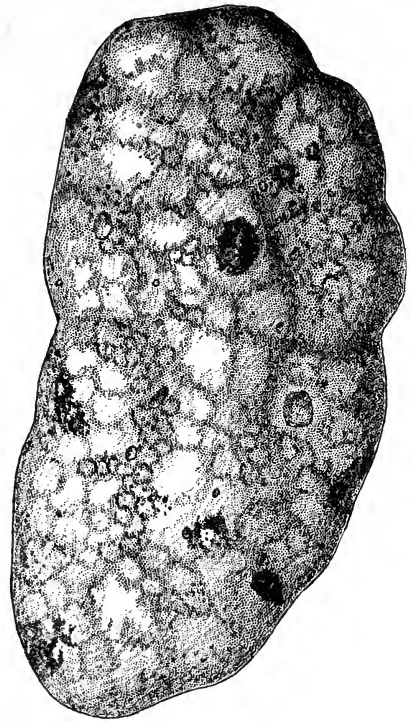


Fig. 322.—Kidney Showing Chronic Interstitial Nephritis. (Natural size.)
The surface is granular and slightly lobulated. The process depicted in this organ is not so advanced as that shown in figure 323.

Chronic interstitial nephritis,[1] also called *chronic productive nephritis*, *chronic indurative nephritis*, *contracting* or *contracted kidney*, *granular kidney*, *fibroid kidney*, *cirrhotic* or *sclerotic kidney*, *gouty*

[1] See Gaucher and Sargent, "Revue de Méd.," Jan., 1901. Nefedieff, "Annales de l'Inst. Pasteur," Jan. 25, 1901. Herringham, "Brit. Med. Jour.," Feb. 23, 1901. Claude and Burthe, "Biochem. Centralbl.," Feb., 1902. Cyzhlarz, "Wien. klin. Rundschau," 1902, No. 16, p. 299. Herrick, "Jour. Amer. Med. Assoc.," Oct. 4, 1902, p. 838. Tschistovitch, "Bolnitch. Gaz. Bot.," Oct. 23, 1902. Lloyd, "Proceed. of Phila. Co. Med. Soc.," Nov., 1902, p. 291. Silberstein, Inaug. Diss., Berlin, 1903. Elliott, "Chicago Med. Recorder," Oct., 1903, p. 239. Cassel, "Berl. klin. Woch.," 1904, No. 21. Klineberger, "Münch. med. Woch.," Feb. 3, 1904, p. 304. Sawada, "Deut. med. Woch.," March 17, 1904. Beer, "Amer. Jour. of Med. Sci.," April, 1904. Jores, "Virchow's Arch.," 1904, Bd. 178, p. 367. Rohn, "Prag. med. Woch.," 1904, No. 15. Wilson, "Lancet," Oct. 29, 1904, p. 1208. Prym, "Virchow's Arch.," 1904, Bd. 177, p. 485. Hirsh, "Amer. Jour. of Med. Sci.," June, 1904. Thomson, "Med. Record," Aug. 20, 1904, p. 281. Nettleship, "Royal London Ophthalmological Hospital Reports," vol. xvi, p. 1.

kidney, *renal sclerosis*, and occasionally *hob-nail kidney*, is a chronic interstitial inflammation of the organ attended by a notable increase in the intertubular and periglomerular connective tissue.

That the large white kidney, already described, ever becomes converted into the kidney at present under consideration seems highly improbable, and that the small white kidney might eventually terminate in a fibroid organ is not likely. In a large majority of cases, if not in all, chronic interstitial nephritis is primary, and is not preceded by any of the lesions already considered. There may be no apparent cause; heredity is a possible influence; continual excretion of irritant materials is probably the most constant factor; examples of this are to be noted in alcoholics, in sufferers from gout and lithemia, in chronic lead-poisoning, and in individuals who subsist upon a diet composed largely of substances the metabolism of which terminates in uric acid. Persistent overwork of the kidney may be placed among the causes. As to age, the phenomena of the disease usually manifest themselves only in advanced life—forty years or later; the disease is rare in younger individuals; it is probable, however, that the lesions begin much earlier than the clinical data would seem to indicate. Nettleship has been able to collect 80 cases of interstitial nephritis in patients under twenty-one years of age, and Cassel describes an hereditary syphilitic interstitial nephritis occurring in children; Rohn has recorded a case of unilateral contracted kidney in an infant three months old; Hirsh's patients were fifteen and eighteen years respectively. The frequency with which chronic interstitial nephritis and arteriosclerosis are associated, and the fact that the vascular changes within the kidney are essentially the same as those seen in the arteries elsewhere, strongly suggest a close connection between the two conditions. Gull and Sutton were the first to lay particular stress upon the relation between the renal and vascular changes, and to suggest that both were part of a single complex process. At a meeting of the American Medical Association in 1904, Prof. Welch exhibited a kidney the two poles of which were supplied by different arterial branches; one artery showed arteriosclerosis and the corresponding pole of the kidney was granular. Observers agree that it is possible to recognize a form of interstitial nephritis consecutive to vascular disease, and to this type has been given the name **arteriosclerotic contracted kidney.**

Morbid Anatomy.—The kidneys are diminished in size, and may weigh no more than from 100 to 125 grams; both organs may not be equally involved. The surface of the kidney is uneven, irregular, and indurated, and the capsule can not readily be cleared of the perinephric fat. The organ is very firm, is hard and slightly elastic, and resists cutting to such a degree that it may creak under the knife; the color varies—it is usually red or reddish, or, when the kidney is markedly anemic, may be somewhat pale; it never possesses the yellowish, fatty appearance which constantly accompanies chronic parenchymatous inflammation. The capsule usually strips off with great difficulty, and it is firmly adherent to the underlying tissue, part of which commonly is brought away with the capsule. In some cases the newly formed fibrous tissue is not immediately subcapsular, and therefore does not tie the capsule closely to the organ. The capsule is markedly thickened, and immediately under it may be found small cysts varying in size

from the diameter of a pinhead to that of the end of one's thumb, rarely larger; these cysts are near the surface, and may be ruptured in removing the capsule. The cyst contents are usually clear or slightly straw-colored. In very rare cases there may be hemorrhage into or around the cyst.

In comparing the cortex with the medullary portion the observer will be immediately struck with the contrast between the condition now being described and the cortex in chronic diffuse nephritis. The cortex is irregularly thin, and pyramids are observed in which, macroscopically, the medulla appears to extend to the capsule. Occasionally a pyramid possesses its normal quota of cortex, thus illustrating the patchy character of the lesion; as a rule, however, the cortex, covering all the pyramids, is more or less contracted. The pyramids are but slightly wasted. There is usually considerable fat in the pelvis, which is less capacious than normal. That the morbid anatomy of this condition varies could not be better shown than in figures 322 and 323, and Plate XVII, figure 1.

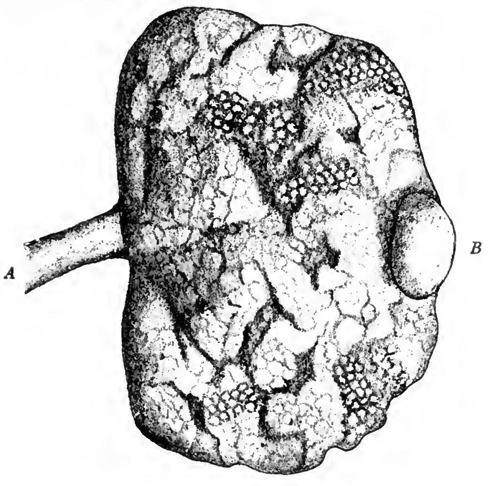


FIG. 323.—KIDNEY SHOWING ADVANCED CHRONIC INTERSTITIAL NEPHRITIS. (Natural size.)

A. Ureter. *B*. Small cyst just under capsule. The irregularly lobulated, coarsely and finely granular surface is well shown.

Histologic examination shows that the lesion is patchy and not universally distributed throughout the cortex; here and there are observed small areas in which the changes are most marked; at other points the structural alterations are inconspicuous. The fibrous tissue is notably increased in the labyrinth, less so in the pyramids of Ferrein, and the medullary portion is changed least of all. Between the tubules, in the interstitial connective tissue of the organ, the fibrous tissue hyperplasia, in various stages of development, is encountered; the more recent cellular accumulations are composed of lymphoid cells. Where organization is in process, the round mononuclear cells will be seen gradually forming into spindle-shaped elements, through the activity of which fibrous tissue is eventually produced. Silberstein has shown that, like other productive interstitial inflammations. renal sclerosis is attended by an increase in the elastica of the organ. The newly formed cicatricial tissue contracts and presses upon the blood-vessels, Malpighian tufts, and tubules, thereby lessening the blood supply, the nutrition, and the functional activity of these structures. The capsules of the glomeruli are thickened by the progressive fibrosis, and the contraction of the newly formed fibrous tissue and hyaline change in the capillaries lead to destruction of the tuft. Glomeruli whose vascular

PLATE XVII.

FIG. 1.

Kidney. Chronic Interstitial Nephritis. See p. 653. (*Atlas of Pathology*, Sydenham Society.)

FIG. 2.

Part of Kidney, Subacute Diffuse Nephritis. See p. 646. From girl 6½ years old. Scarlet fever; death on the forty-seventh day. More advanced degenerative change than in Fig. 4. (*Atlas of Pathology*, Sydenham Society.)

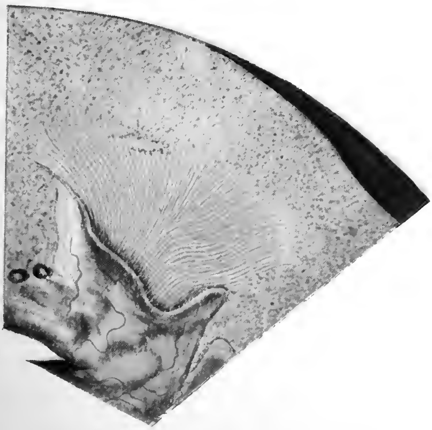


FIG. 3.

Kidney, Chronic Diffuse Nephritis. See p. 649. (*Atlas of Pathology*, Sydenham Society.)

FIG. 4.

Part of Kidney, Acute Diffuse Nephritis. See p. 645. From boy 9 years old. Scarlet fever; death on the twenty-second day of the disease. The initial stage of engorgement is no longer present. (*Atlas of Pathology*, Sydenham Society.)

supply is still normal possess thickened capsules; the thickening of Bowman's membrane is continuous with the thickened membrana propria of the tubule. The epithelium of the tubules shows various changes dependent upon the influence of the interstitial deposit within any given area. The large, swollen, granular, fatty, tortuous tubules of parenchymatous nephritis are not encountered; in those areas in which the new tissue is most rapidly organizing the tubules are diminished in size. Tubular narrowing in one area may give rise to dilatation in another, and by progressive widening terminate in the formation of the cysts already described when discussing the gross anatomy of the lesion. Cornil and Ranvier asserted that such cysts might arise

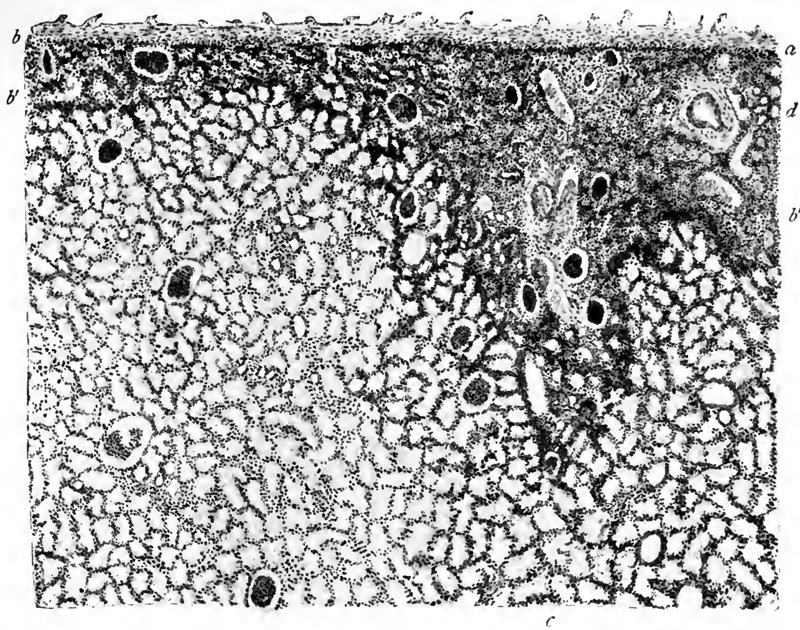


FIG. 324.—KIDNEY, CHRONIC INTERSTITIAL NEPHRITIS. (¼-inch objective, 1-inch ocular, slightly reduced.) Specimen fixed in corrosive sublimate, infiltrated with paraffin, and stained with hematoxylin and eosin. *a*. Slightly thickened capsule. *b*, *b'*, *b''* and *a* bound the area of most marked interstitial change, although an increase of the interstitial tissue is evident between *b''* and *c*. About one centimeter to the left of *d* is seen a beginning cyst. In the area of most marked interstitial change are a number of degenerating Malpighian tufts, while but a few of the tubules are recognizable. The new tissue is not yet fully developed, but at points, as around the cyst *d*, shows partial conversion into fibrous tissue.

from the Malpighian tufts—a view which has been corroborated by later studies, especially by Beer. The condition is termed cystic atrophy of the glomeruli. In the glomerular cysts, shrunken fragments of the tuft are sometimes found still attached to the inclosing wall. Where the tubule is subjected to the damaging influence of contraction, the epithelium is atrophied and finely granular, and the cells are greatly diminished in size; where the fluids are retained within the tubule by obstruction below, the epithelium is flattened, hyaline, granular, or even fatty. Occasionally, tube-casts may be seen *in situ;* if the epithelium or interstitial tissue be pigmented, it is probably the result

of previous hemorrhage. The blood-vessels of the kidney manifest changes indistinguishable from those observed in similar structures elsewhere.

The *urine* is increased in quantity, light in color, and may be almost colorless; its specific gravity is rarely over 1012 or 1015, and may fall as low as 1005; albumin is present in varying amounts; sometimes the albumin may be scanty and may escape detection, or, for short periods, rarely long, it may be entirely absent; as a rule, there is no sediment, and the dissolved solid constituents—salts and urea—are diminished. The casts found are usually hyaline; they are not abundant and not constantly present; during acute exacerbations in the inflammatory processes the phenomena of nephric hyperemia may be observed.

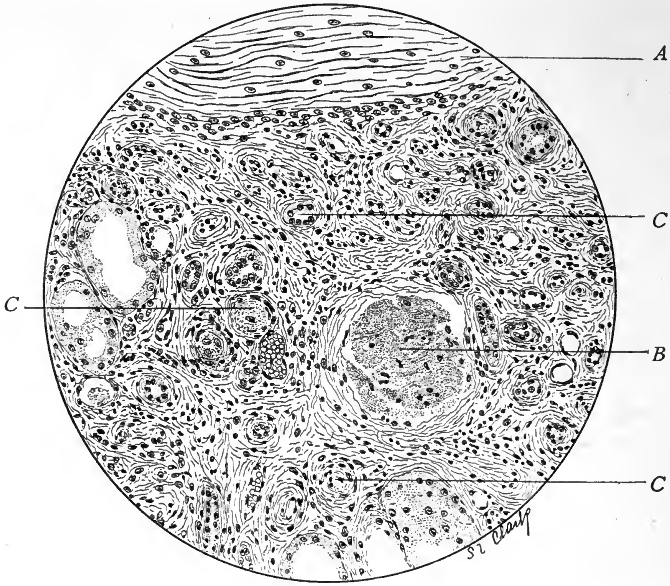


FIG. 325.—KIDNEY, CHRONIC INTERSTITIAL NEPHRITIS.
A. Part of capsule. *B*. Malpighian body, showing advancing granular and hyaline changes with marked thickening of the capsule. *C*, *C*, *C*. Tubules in the midst of the newly formed connective tissue; the epithelium is wasted or absent and the tubular wall notably thickened. The larger tubes on the left and below are somewhat dilated.

Changes Occurring in Other Structures.—Clinicians have long known that the arterial tension is raised, at least in the earlier stages of chronic interstitial nephritis, and more recently Czyhlarz, Sawada, and others have studied the elevated tension by instrumental methods. Czyhlarz believes that he has been able to show that with improvement the arterial tension falls, and rises again during relapses. It is not certain, however, that the alteration in tension may not be due to the vascular, rather than the renal, lesion. Cardiac hypertrophy is constantly present prior to degenerative or arteriosclerotic changes in the myocardium, after which dilatation occurs. As a result of the accumulation of toxic products, uremic phenomena are not infrequent; these may be manifested by symptoms referable to the vascular and

toxemic influences on the central nervous system, or by less definite nervous symptoms which Lloyd refers to as hysteric or neurasthenic. Neuritis is occasionally observed. De Schweinitz[1] describes with detail the retinal lesions to which the term albuminuric retinitis is commonly applied. The vessels of the retina may be the seat of recognizable arteriosclerotic changes. According to Nettleship, the earliest age at which renal retinitis has been observed is five years.

Lardaceous disease of the kidney arises in connection with general amyloid disease. (See p. 227.) The process is frequently associated with a more or less fully developed chronic parenchymatous nephritis, of the kind already described.

Morbid Anatomy.—In many cases the kidney is considerably increased in size; occasionally it may not be larger than the normal;

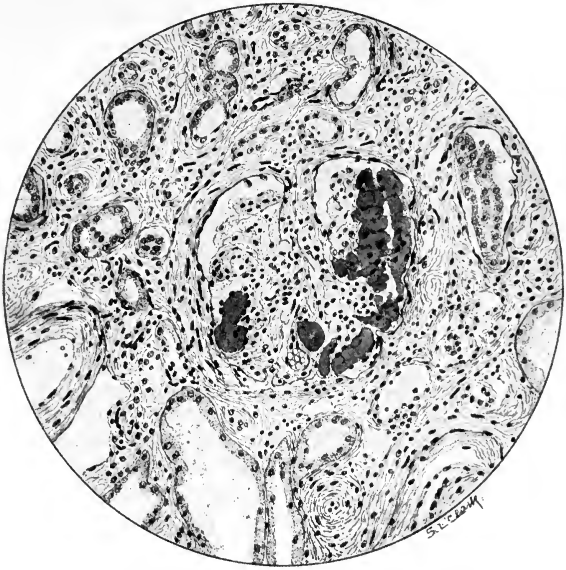


FIG. 326.—KIDNEY, CHRONIC INTERSTITIAL NEPHRITIS AND LARDACEOUS DISEASE.
Specimen specially stained by gentian-violet. *A*. The thickened capsule of a Malpighian tuft; the interstitial tissue at all points in the field is notably increased. *B*. In that part of the tuft lying to the right and below the tuft pedicle, and indicated by the faint leader from *B*, the opaque lardacein can be seen.

in rare instances the organ is small. The veins of the capsule are dilated the surface is smooth, and the organ is firm, but does not appear fibroid. The tissue cuts with more resistance than in uncomplicated chronic parenchymatous nephritis; the cortex is much thickened, is glistening or hyaline, is slightly swollen, and the Malpighian tufts, in which the lesion is most manifest, may be readily picked out. The pale, hyaline, or semitranslucent cortex contrasts with the deep-red or, at times, almost purplish, or beefy, medullary portion; the usual tests for lardacein readily demonstrate the character of the lesion.

The urine is usually abundant, pale, clear, and of a low specific gravity; albumin and also hyaline, granular, or fatty casts are fre-

[1] "Proc. Phila. Co. Med. Soc.," Nov., 1902, p. 298.

quently present, and, occasionally,—not constantly, as commonly believed,—waxy casts which may give the amyloid reaction. The changes in other organs and tissues are dependent upon the general amyloid infiltration or upon the character of the accompanying renal lesion If the condition be attended by diffuse nephritis, dropsy, edema etc., may be present; if the accompanying lesion be an interstitial nephritis, which is rare, the vascular and other phenomena of that condition may be manifest.

Pyelitis[1] is an inflammation of the pelvis of the kidney. It may be acute or chronic; primary or secondary—rarely the former. It may result from extension of an infection from the kidney, but more commonly it is the cause of inflammation extending into the medulla or the cortex.[2] Inflammation of the renal pelvis is usually the result of infection by bacteria excreted by the kidney; in other words, it is indirectly of hematogenous origin. The belief that infections of an ascending type, secondary to disease of the bladder, are of common occurrence, is less popular than formerly. The experiments of Sampson seem to indicate that overdistention of the bladder never gives rise to dilatation of the ureters; this, however, does not disprove the possibility of inflammation extending along the course of the continuous mucosa. The bacteria commonly found are the typhoid bacillus, the colon bacillus, and the pyogenic cocci. Wright reported a case in which the influenza bacillus was present with other organisms. The combined statistics of several observers show that the colon bacillus occurs in about 83.5 per cent. of the cases. Pneumococcal forms have been described. Probably the most important factor in the production of pyelitis is ureteral obstruction. Kinks, inflammatory conditions, or external pressure, producing accumulations of urine in the pelvis of the kidney, are commonly followed by pyelitis. It is now generally believed that the pyelitis of pregnancy results from obstruction due to pressure on the ureter by the gravid uterus. The pyelitis of infants is probably due to some congenital abnormality that produces temporary urinary stasis. Among the rare causes of inflammation of the pelvis of the kidney may be mentioned perinephritis and inflammations around the ureter (periureteritis) and morbid growths invading the affected structures. Stone in the kidney (nephrolithiasis) is commonly given as a cause of pyelitis, but it is probable that stone is a sequence of pyelitis, and not the reverse. It is said that the administration of turpentine, cantharidin, and other irritating agents may produce inflammation of the renal pelvis.

The inflammation may be catarrhal, pseudomembranous, suppurative, or hemorrhagic; rarely it is gangrenous. The first three forms

[1] Brown, "Johns Hopkins Hospital Reports," vol. x, Nos. 1 and 2. Caro, "Deut. med. Woch.," April, 1901. Thomson, "Edinburgh Obstet. Soc.," April 4, 1902; also "Brit. Med. Jour.," May 31, 1902, p. 1338. Hartwig, "Berl. klin. Woch.," Nov. 20, 1903. Bazy, "La Presse Méd.," Dec. 30, 1903, p. 893. Haberlin, "Münch. med. Woch.," Feb. 2, 1904, p. 198. Cathala, "Thèse de Paris," 1904. Sampson, "Johns Hopkins Hosp. Bull.," 1903, vol. xiv, p. 334. Cragin, "Med. Record," July 16, 1904, p. 81. Rochard, "La Presse Méd.," Nov. 16, 1904, p. 729. Spalding, "Jour. of Obst.," Feb., 1905. Wright, "Boston Med. and Surg. Jour.," April 27, 1905, p. 496. Elliott, "Med. News," Aug. 20, 1904, p. 357. Keyes, "N. Y. Med. Jour.," Aug. 27, 1904, p. 397.

[2] See Acute Suppurative Interstitial Nephritis, p. 641.

may be acute or chronic; the last two are usually acute, but may be engrafted upon one of the chronic forms. The inflammation may partake of some of the characters of the acute infectious disease with which it is associated; thus, gonorrheal pyelitis is commonly suppurative. I have seen membranous pyelitis accompany diphtheria and also typhoid; with the last-named disease hemorrhagic forms sometimes occur. If ureteral obstruction takes place, dilatation of the pelvis and pressure atrophy of the kidney give rise to a sac in which the purulent matter and altered secretions accumulate; the condition is called **pyonephrosis,** and may also result from infection of a hydronephrosis. The fluid contained in the sac, which may be loculated and composed of several pouches, often appears to be almost pure pus, although usually urine is present and sometimes blood. Calculi which have preceded the suppurative process may also be found. The changes in the renal tissue depend upon the duration and character of the inflammation and also upon whether actual infection of the kidney substance has occurred. The lesions of acute suppurative nephritis may be present or the renal parenchyma may be thinned and fibroid and contain no foci of pus-formation. Sometimes no macroscopically perceptible kidney tissue is present. The condition may be attended by a perinephritis (see p. 634).

Nephrolithiasis is a name applied to a condition in which stones are present in the kidney. In size such bodies vary from fine granules deposited in the tubules to large masses that fill the renal pelvis; Shield reported a renal calculus weighing 485 gm. The stone may be solitary, or calculi may be present in large numbers. Bland-Sutton[1] reports an instance in which 40,000 iridescent calculi were contained in a single kidney. Renal stones are usually composed of uric acid or urates, oxalate or phosphate of lime, and less frequently carbonates, cystin and xanthin, and rarely indigo. Each concretion usually possesses a nucleus surrounded by lamellæ, all of which may not be of the same chemic composition. Ova of the Bilharzia hæmatobia may constitute the nucleus. Frequently the nuclei contain bacteria, and some observers maintain that germs are the essential cause of calculus formation. This contention is supported by the well-known frequency with which microorganisms are responsible for the production of gall-stones. Obstruction to the ureter and inflammation of the pelvis of the kidney favor the development of calculi. Such stones are called secondary calculi. It is supposed that nephrolithiasis may occur without any preceding inflammation of the pelvis of the kidney, and stones thought to have this origin are termed primary calculi.

Calculi arising in the pelvis of the kidney may obstruct the ureter and give rise to retention, or by favoring colonization of pyogenic bacteria induce suppurative pyelitis or pyelonephritis, which may, in some cases, become gangrenous. More or less hematuria accompanies the presence of stones in the renal pelvis, and some observers maintain that, in all cases, a careful search will disclose the presence of red blood-cells in the urine. It is possible that loculated calculi (those definitely inclosed in a renal pouch) are infrequent causes of hemorrhage.

Ureteritis, or inflammation of the ureter, probably results from

[1] "Brit. Med. Jour.," Jan. 31, 1905, p. 125.

essentially the same causes as pyelitis, and may be a continuation of, or antecedent to, the latter. Occasionally inflammation begins at the cystic end of the ureter and is secondary to inflammation of the bladder. The well-known frequency with which bacteria occur in the urine (bacteriuria) accounts for many of these cases. Traumatic forms are rare; ureteritis due to disease of the prostate or ureteral orifice is of frequent occurrence. The inflammation may be acute or chronic, and may first affect the mucosa or the ureteral wall, and from either involve the contiguous tissues, causing **periureteritis.** The acute form of the affection may be catarrhal, pseudomembranous, suppurative, or gangrenous; fibrinous casts of the ureters are sometimes voided. When the inflammation is of long duration, great thickening of the ureteral wall and stricture formation may occur. A **cystic ureteritis,**[1] due to central degeneration and fluid transudation into v. Bruns' cell-nests, has been described. The resulting cysts resemble miliary tubercles and may give rise to obstruction. Strictures, kinks, and valve-like formations may produce ureteral obstruction and give rise to cystic dilatation on the renal side of the lesion, which will be further discussed with hydronephrosis.

Tuberculosis is not an infrequent form of ureteral disease and will be considered with tuberculosis of the kidney.

Tuberculosis of the kidney[2] may be primary or secondary. The primary form is rare. Morris has been able to collect 15 such cases in 2610 autopsies. Infection may occur from the blood or by an ascending tuberculosis which was primary in the lower passages. In the discussion of the German Surgical Congress in 1901, Baumgarten doubted the frequency of ascending infections, and it is generally conceded that tuberculosis, involving the genito-urinary organs, usually begins in the kidney. It has been shown by a number of observers that in patients suffering from active tuberculosis[3] the bacilli may be secreted in the urine.

In acute miliary tuberculosis the kidney in common with other organs frequently contains large numbers of tubercles. These bodies possess the usual characters of miliary tubercles observed elsewhere (see p. 149). In other cases the kidney contains a single caseous nodule surrounded by fibrous tissue which is sometimes calcareous; rarely such masses are bilateral and multiple in both organs. In the so-called **massive tuberculosis of the kidney** practically the entire organ is converted into caseous material. This form, more frequently than the preceding types, is accompanied by tuberculosis of the pelvis and ureter and may involve the bladder. The organ is often greatly enlarged, and may be the size of a fetal head; the capsule is usually thickened and the perinephric fat sclerosed. In some cases tuberculous perinephritis accompanies the renal lesion. Usually this form is unilateral and the opposite kidney is not infrequently amyloid. Often the discharge of caseous material obstructs the ureter, or ureteral stenosis results from tuberculosis of the ureteral mucosa. In such cases, par-

[1] See Carey and Laird, "Albany Med. Annals," July, 1904; bibliography.

[2] The important literature on the subject is given by Douglas, "Surgical Diseases of the Abdomen," 1903, p. 552.

[3] Flick and Walsh, "Proceed. of Path. Soc. of Phila.," April, 1903, p. 149; see also discussion, p. 154.

ticularly if mixed infection be present, the resemblance to pyonephrosis is striking. Israel[1] states that in thirty-three per cent. of the cases of pyelitis with retention of pus tuberculosis of the affected organ complicates the primary lesion. Chronic caseous tuberculosis of the kidney is often latent and frequently comes to autopsy undiagnosticated.

Syphilis of the kidney, manifested by distinct lesions, is of infrequent occurrence. Syphilitics in whom the tertiary phenomena are active, may have amyloid disease of the kidney, and during the secondary stage true syphilitic nephritis sometimes occurs. The arterial lesions due to syphilis may affect the kidney, giving rise to a form of arteriosclerotic contraction. Gummata of the kidney are rare, and when present possess the usual characters of the syphiloma. (See p. 179.)

Leprosy rarely gives rise to distinctive alterations in the kidney; patients affected with the disease not infrequently develop nephritis, probably due to the continuous secretion of irritants resulting from lesions outside the kidney.

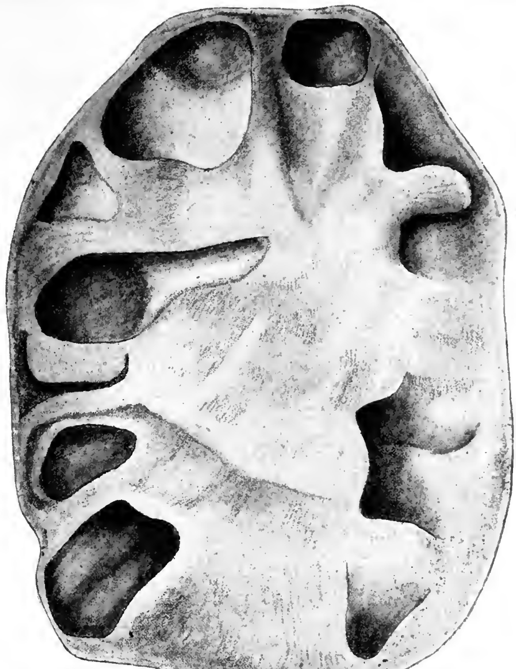


FIG. 327.—TUBERCULOUS PYELONEPHRITIS; CHRONIC TUBERCULOSIS OF THE KIDNEY.
Specimen shows cavities in medullary and cortical portions of the organ due to the extension of tuberculosis from the pelvis.

Tumors of the kidney[2] are not common. Of 159 cases collected by Morris, 63 were sarcomata, 41 carcinomata; his list also includes 21 instances of cystic degeneration and 11 hydatid cysts; there were 10 adenomata. Of the *sarcomata*, seventy-five per cent. occur in infancy; occasionally they are congenital and may obstruct labor. Some of the sarcomata are histologically extremely complex, often containing structures that suggest adenoma or carcinoma, and have been called **adenosarcomata** of the kidney. Birch-Hirschfeld has especially called attention to such neoplasms.[3] *Angiomata*, *leiomyomata*, and *rhabdomyomata* of the kidney are rare. **Angiomata** have been observed; they sometimes involve the pyramids or the pelvis, and may give rise to troublesome hemorrhage.

[1] "Deut. med. Woch.," vol. xxiv, p. 442.
[2] Albarran and Imbert, "Tumeurs du Rein," 1903.
[3] See also Strong, "Arch. of Pediatrics," May, 1903, p. 321; Blumer, "Albany Med. Annals," Aug., 1903, p. 444.

Papilloma[1] of the pelvis of the kidney may be extremely small, but attended by hemorrhages that prove fatal; it is usually of the villous type.

Probably the most frequent tumor of the kidney is the **hypernephroma,** a neoplasm arising from ectopic adrenal tissue. Of the 163 hypernephromata collected by Ellis,[2] 157 were in the kidney. There is no special predilection for either side; the tumors are usually soft, sometimes cyst-like. The neoplasm is often sharply outlined from contiguous tissue, and usually possesses a capsule. Some give rise to metastasis, others do not, and it has been suggested that benign and malignant hypernephromata be recognized. Histologically these neoplasms are composed of cells resembling those seen in the adrenal;

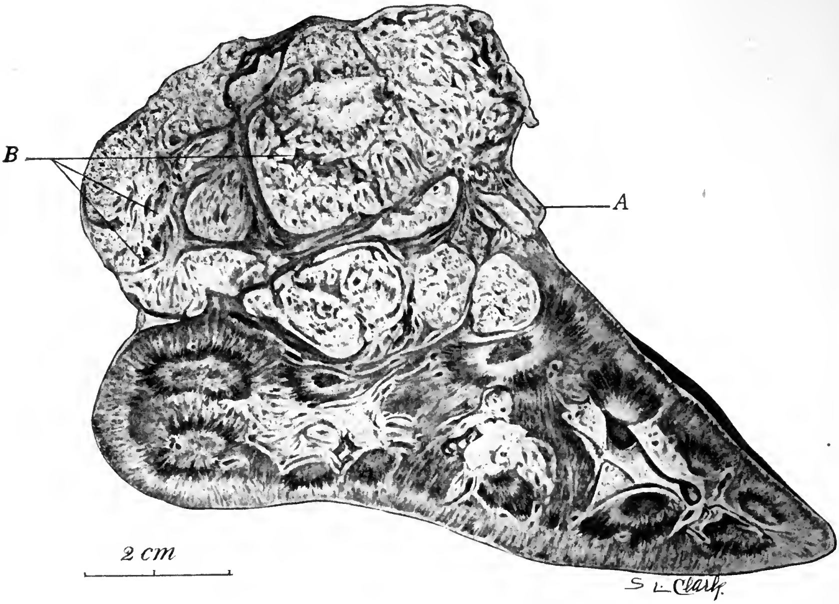


FIG. 328.—HYPERNEPHROMA. (CASE REPORTED BY KEEN.)
A. Capsule of kidney over tumor. *B*. Areas of hemorrhage.

they usually contain a fairly uniformly distributed stroma, which in many areas is scant and often extends into relatively large spaces, indicating that under certain conditions it is ruptured or in other ways disappears before the rapidly growing cell. Such extensions of the stroma are covered by the large vesicular neoplastic cells, giving rise to a picture resembling that of papillary adenoma. Hemorrhage in the interior of the tumor is not uncommon.

[1] Butte, "Virchow's Arch.," 1901, Bd. 164. Savory and Nash, "Lancet," Dec. 17, 1904, p. 1699.

[2] For detailed study of these neoplasms and references to literature see Keen, Pfahler and Ellis, "Amer. Med.," Dec. 17, 1904.

Paranephric tumors[1] are rarely primary; they may be due to extension from contiguous structures, especially the kidney or adrenal.

Cysts of the Kidney.—Retention cysts of the renal tubules occurring in contracted kidney were considered with interstitial nephritis. In the cortex they are commonly small, although they may be as large as the end of one's thumb, rarely larger. They are usually multiple and result from occlusion of the tubules with dilatation above the obstruction, or from cystic atrophy of the tufts.

Hydronephrosis[2] is a condition resulting from ureteral obstruction, and is characterized by more or less distention of the renal pelvis and coincident atrophy of the medulla and cortex. The affection may be congenital or due to developmental abnormalities, such as partial or

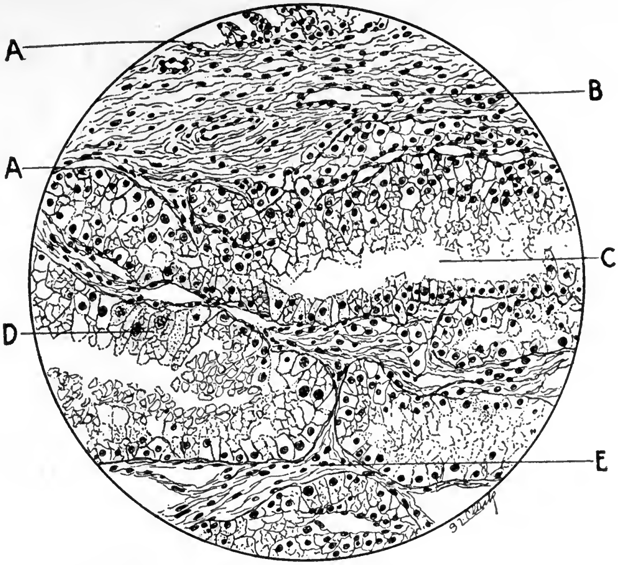


FIG. 329.—SECTION OF HYPERNEPHROMA, SHOWING CAPSULE.

A to A. Capsule. B. Blood-vessel in capsule. C. Alveolus surrounded by polyhedral cells, many of which are polymorphous and possess the general characters of the cells found in the adrenal cortex. D. Typical spongiocyte. E. Connective-tissue reticulum.

complete atresia of any part of the conducting passage. Many writers lay great stress upon oblique or valve-like junction between the ureter and renal pelvis as a cause of hydronephrosis; the condition may be produced by tortuosity and kinks of the ureter. Strictures of the urethra or ureter, and renal or ureteral calculi, may also give rise to hydronephrosis. Tumors involving the ureter or its orifice in the bladder, or neoplasms pressing upon the duct, may also produce retention. Prolapsed or floating kidneys not uncommonly show moderate degrees of hydronephrosis. The amount of distention and consequent

[1] Rambaud, "Thèse de Toulouse," 1904.

[2] Riesman, "Proceed. of Path. Soc. of Phila.," July 15, 1898, p. 253. Bazy, "Revue de Chir.," Jan. 10, 1903, and "La Presse Méd.," Aug. 3, 1904, p. 489.

size of the affected organ are largely influenced by the completeness and persistency of the obstruction. If the ureter be ligated, or in

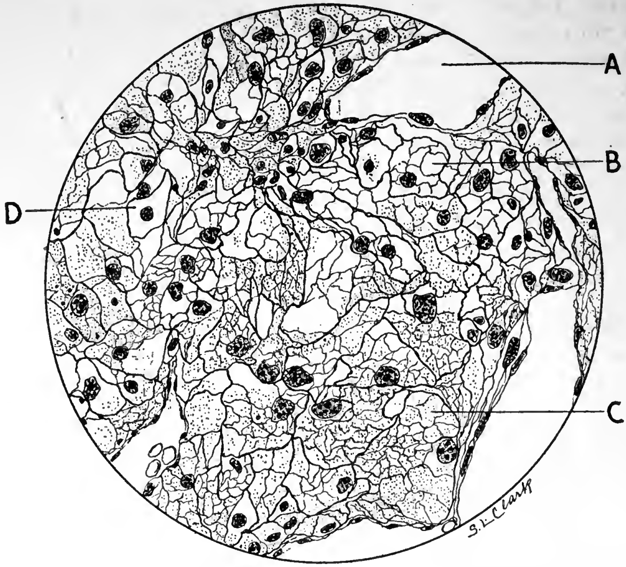


FIG. 330.—SECTION OF HYPERNEPHROMA, SHOWING CHARACTER OF CELLS. SAME SECTION AS FIG. 329. (Zeiss 2 mm. homo. im.)

A. Blood-vessel. B and C. Spongiocytes. In the upper cell (B) the intraprotoplasumic spaces appear empty; the corresponding areas in the lower cell (C) contain faintly acidophilic fine granules. D. Similar cell, with structureless clear protoplasm.

other ways suddenly occluded, renal atrophy without notable increase in the size of the organ commonly occurs. If, however, the obstruction

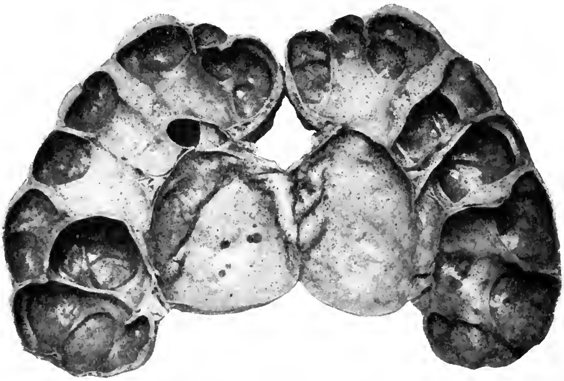


FIG. 331.—HYDRONEPHROSIS.

Kidney laid open, showing both halves. A few small, calcareous nodules in the pelvis. (From a photograph made by Dr. I. W. Blackburn, to whose courtesy the writer is indebted for the use of the illustration.)

develops slowly, or is intermittent in its action, cysts of very great size may result. Infection may convert the hydronephrotic kidney

into a pyonephrosis. Morris includes pyonephrosis and hydronephrosis under the term **renal distention** or **nephrectasis.**

Hydatid cysts[1] **of the kidney** are infrequent. Of Lyon's 241 cases of echinococcal disease in America, in 9 the kidney was involved. The left kidney is affected nearly twice as often as the right. The condition may be accompanied by hematuria, the urine containing hooklets, less commonly scolices, and in rare instances small cysts or fragments of the cyst-wall.

Under the name **cystic disease of the kidney,**[2] **polycystic kidney,** *cystic degeneration of the kidney*, or *conglomerate renal cysts*, there has been described a peculiar lesion manifested by the presence of large multilocular cysts occupying the area of and replacing the kidney, but frequently containing no discernible renal tissue. In other instances but part of the kidney is involved. In bilateral cystic disease the

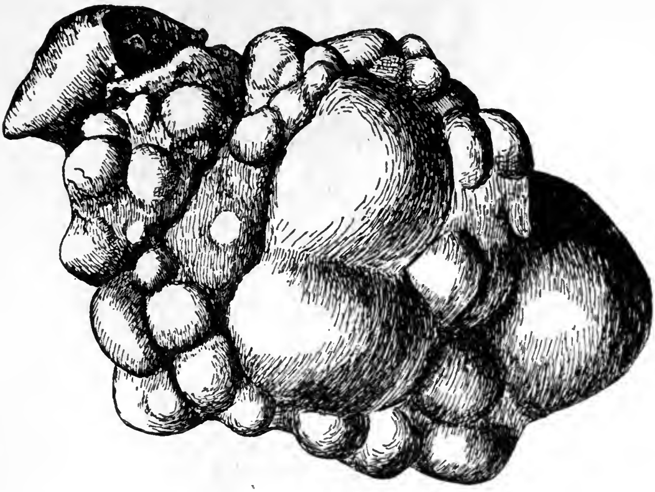


FIG. 332.—CONGENITAL CYSTIC DISEASE OF THE KIDNEY. (Natural size.)
(From specimen presented by Dr. E. E. Graham. Original article in "Archives of Pediatrics," October 1899. Figures 333, 334, 335, and 336 are from the same specimen.)

involved organs may be so large as to impede labor; Fussell collected 11 cases in which it was necessary to mutilate the fetus in order to accomplish delivery. The tumors in the adult may be of enormous bulk. In Hare's case the left kidney weighed 7 kilos. A specimen in the Museum of the Jefferson Medical College is considerably larger than a fetal head. The organ was removed postmortem, and, during

[1] Paton, "Lancet," Jan. 21, 1905, p. 159. Haynes. "Annals of Surgery," July, 1902. See also p. 199.
[2] Howard, "Cleveland Jour. of Med.," July, 1900. Fels, "Münch. med. Woch.," Oct. 21, 1902, p. 1743, and Oct. 28, 1902, p. 1799. Boinet and Rayboud, "Rev. de Méd.," Jan., 1903. Pettersson, "Zieg. Beitr.," 1903, vol. 33, p. 605. Morse, "Jour. Amer. Med. Assoc.," Dec. 19, 1903, p. 1537. Blackburn, "Trans. of Path. Soc. of London," 1904, vol. 55, p. 203. Busse, "Virchow's Arch.," 1904, Bd. 175, p. 442, and "Deut. med. Woch.," 1904, No. 4.

life, had given rise to but slight inconvenience, not at all lessening the comfort or usefulness of a physician throughout a long and active professional career. Commonly the appearance suggests cyst formation beginning in the cortical portion of the organ, and, when the subject has survived to adult life, the cysts may be restricted to that structure. The cystic kidney is large, made up of numerous cysts, and often shows no recognizable renal tissue; the fluid within the cyst is usually clear, slightly if at all albuminous, and the urinary constituents present may be no more abundant than in cysts of other organs. Cholesterin is commonly present, and the cyst may contain a trace of blood pigment,

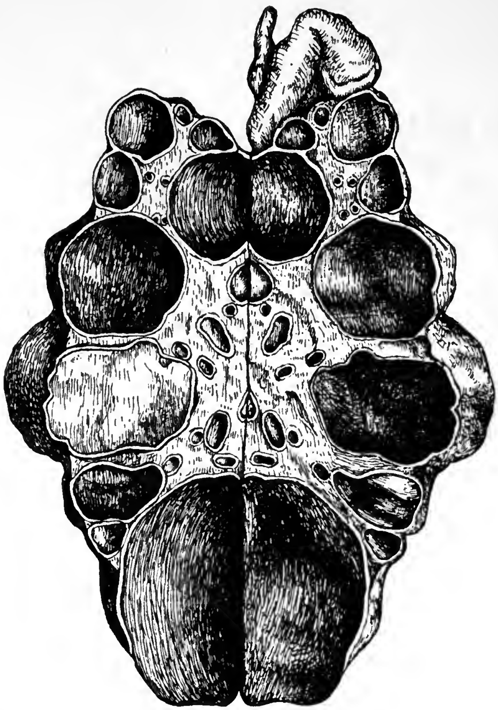


FIG. 333.—KIDNEY, CONGENITAL CYSTIC DISEASE; LAID OPEN. (Same case as Fig. 332.)

and not infrequently detritus resulting from degenerative and necrotic processes in the epithelium of the cyst-wall. Sometimes the connective-tissue wall of the cyst is not covered by a recognizable epithelial lining. In other instances there is a varying amount of epithelium, which may be granular and necrotic; and in still other specimens low or tall columnar epithelial cells form the inner layer of the cyst-wall. A study of these cysts in various stages of evolution leads to the belief that primarily they all possessed an epithelial lining. The matrix between them may be fibrous or myxomatous, and is not infrequently extremely vascular.

Our knowledge of the etiology of these congenital cysts is by no means satisfactory. Virchow believed that they were due to a dilatation

FIG. 334.—CONGENITAL CYSTIC DISEASE OF THE KIDNEY. (Tissue from near the pelvis of the kidney shown in Fig. 332.)

A. Distended blood-vessel. *B*. Connective tissue similar to that shown at *C* in figure 336. In many areas this connective-tissue matrix is made up of multipolar or branching cells, such as occur in myxomatous structures. Below the blood-vessels are shown transverse and oblique sections of tubules that resemble, to a certain extent, sweat-glands. (1/6-inch objective, 1-inch ocular.)

of the uriniferous tubules resulting from a possible prenatal inflammatory condition. Goodhart suggested that they were examples of renal

FIG. 335.—CONGENITAL CYSTIC DISEASE OF THE KIDNEY.

Section of cyst showing columnar cell-lining and contained detritus; the latter, from a study of other sections seems to be the fragmented cytoplasm of degenerated epithelial cells cast off from the cyst-wall. The section is from the kidney shown in figure 332. (1/6-inch objective, 1-inch ocular.)

adenoma, and in this view was supported by the observations of Bateman. As a result of a careful histologic and embryologic study, Shattock

came to the conclusion that the condition depended upon the maldevelopment of the mesonephron, or Wolffian body, fused with the metanephros, and that the cysts resulted from evolutionary changes in the

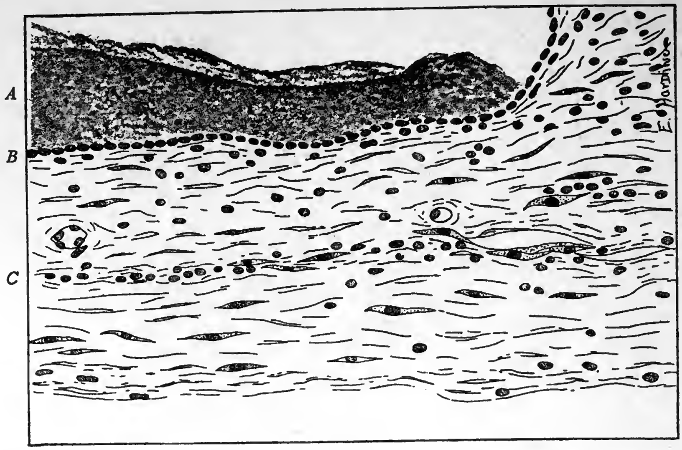


FIG 336.—CONGENITAL CYSTIC DISEASE OF THE KIDNEY. PART OF WALL OF A LARGER CYST. Section of the kidney shown in figure 332. *A*. Granular detritus composed of hyaline material and acidophilic granules. *B*. Flattened epithelium. (Compare with columnar cell-lining of smaller cyst, Fig. 335.) *C*, Connective tissue between cysts. (½-inch objective, 1-inch ocular.)

included mesonephron. At the present time the bias of opinion seems to be toward Shattock's view; their congenital or embryonic origin is generally conceded.

DISEASES OF THE BLADDER AND URETHRA.

The malformations of these organs have already been referred to on p. 633. In the female the bladder may prolapse, constituting a condition called **vaginal cystocele.** Frequent overdistention and straining during urination, associated with relaxation of the abdominal wall, may cause the bladder to protrude in the median line (**abdominal cystocele**). As a result of frequent overdistention, and sometimes from other causes, the vesical wall is greatly thinned (**mural atrophy**). The organ may be small and contracted, but it is probable that this condition is congenital or the result of abnormal irritability, and in either case should not be called vesical atrophy.

In the condition known as **atony of the bladder** it is supposed that the relaxation is due to insufficient tone in the muscle. In such cases degenerative changes in the atrophic fibers have been described

Chronic congestion of the bladder, and also the presence of Bilharzia hæmatobia, may be attended by conspicuous overdistention of the veins. Thrombosis of the pelvic veins, cirrhosis of the liver, and chronic heart disease may also give rise to venous dilatation, sometimes called **vesical hemorrhoids.** Hemorrhage into the bladder wall or submucosa may be due to injury, sometimes follows labor,—in which case it is the result of pressure of the fetal head or instruments,—and is also seen in

hemorrhagic diseases. It is possible that such hemorrhages may become infected and give rise to extending necrosis; such a process may account for ruptures of the bladder observed in the women dying during the puerperium.

Hypertrophy of the bladder may be produced by any condition causing slowly progressing obstruction of the urethra or vesical outlet. In such cases the increased resistance to the outflow of urine induces a gradual hypertrophy of the muscle composing the bladder wall, which, when contracted, may measure 1.5 cm. The hypertrophy is especially marked in prostatic enlargement. Frequently the overgrowth of muscle is not uniform, or as a result of weakening the mucosa pouches at points, giving rise to a ribbed interior.

Cystitis, or **inflammation of the bladder,** may be acute or chronic. It is possible to produce inflammation of the mucosa lining this viscus by the administration of cantharides or turpentine and other irritants excreted by the kidney; the most frequent cause is infection.[1] It is possible that bacteria may reach the viscus from the kidney or through the vessels in the submucosa; they are most frequently introduced, however, from the urethra, and especially by instruments. The microorganisms usually found are the colon bacillus, staphylococci, and streptococci; the typhoid bacillus may also be a cause. When complicating gonorrhea, cystitis is frequently due to the gonococcus, although often the infection is multiple. Any condition (paralysis, stricture, enlarged prostate) which prevents the bladder from fully emptying, favors accumulation of bacteria and their products, and commonly leads to cystitis. When the inflammation has persisted for some length of time, the infection is usually polymicrobic. A special form of cystitis accompanies venal distomatosis.[2]

Morbid Anatomy.[3]—The changes observed are those commonly occurring in inflamed mucous membranes. The inflammation may be catarrhal, suppurative, hemorrhagic, gangrenous, or pseudomembranous, and the frequency with which each form occurs corresponds to the order in which I have named them. Motz and Denis have shown that the subepithelial infiltration is often extensive and the epithelial desquamation less abundant than we had previously believed. Even in catarrhal processes marked dilatation of the vessels, extensive leukocyte migration, and sometimes slight escape of red blood-cells occur. Such changes account for the intense redness of the affected mucous membrane. In the suppurative cases minute abscesses may be formed in the submucosa, and the number of leukocytes observed in the urine is much greater than in any other form of cystitis. According to Parodi,

[1] Experimental and laboratory studies of the flora found in cystitis have been extensive. The important observations will be found in, or may be traced from, the following references: Hofmann, "Centralbl. f. Grenzgebiet. der Med. u. Chir.," vol. vii, No. 20. Baisch, "Beitr. z. Geburts. u. Gynäk.," 1904, Bd. viii, H. 2. Breton, "Gaz. des Hôp.," 1902, vol. 5, p. 533. Paton, "Jour. of Path. and Bact.," Sept., 1902, p. 280. Stokes, "Jour. Amer. Med. Assoc.," Sept. 27, 1902, p. 733. Mellin, "Jahrb. f. Kinderheilk.," 1903, vol. lviii, p. 40. Zelenski, "Wien. klin. Woch.," Feb. 4, 1904, p. 123.

[2] Goebel, "Deut. Zeit. f. Chir.," Bd. 66, H. 3 and 4. Milton, "Lancet," March 28, 1903, p. 866. See also p. 193.

[3] Motz and Denis, "Annals des Mal. Gen. Urinaires," 1903, vol. xxi, No. 12. Parodi, "Arch. per le Sci. Med.," 1904, vol. xxviii, fasc. 1. Hofmann, "Wien. klin. Rundsch.," 1904, No. 49. Dean, "Practitioner," June, 1904, p. 907.

the so-called cystic inflammation of the bladder results from degenerative changes in the inflamed mucosa; the resulting miliary cysts are most abundant in the posterior and superior portions of the organ. In gangrenous cystitis large areas of the mucosa undergo necrosis, the tissue death frequently extending into the muscular layer and sometimes perforating. It is usually an evidence of intense infection, and commonly occurs in the debilitated. The so-called pseudomembranous cystitis is rarely attended by the production of a false membrane comparable to that seen on other mucosæ, although the macroscopic resemblance may be strong. Dean's examination of the specimen from his patient corroborated Adami's view that the disease depends upon a superficial necrosis of the mucosa. In the chronic inflammations of the bladder there is often notable thickening of the mucosa and submucosa, and in some cases a perceptible increase in the muscle layer. The studies of Tyler, Brown, and also Stokes, seem to disprove the prevailing belief that the urine is alkaline in cystitis. The percentage of cases in which normal acidity disappears is small. The vesical changes accompanying venal distomatosis will be found described on page 194. Cystitis is not infrequently followed by inflammation of the ureter, and may precede or follow prostatitis. Inflammation around the bladder (**pericystitis**) may be secondary to intracystic processes, or results from inflammatory conditions arising in contiguous structures.

Vesical calculi may be composed of uric acid or its salts and the salts of calcium, especially the carbonates, phosphates, and oxalates. The concretions vary in size from small particles, so-called *vesical sand*, to masses weighing 100 gm. or more. They are particularly prone to form around foreign bodies. It is probable that the formation of concretions within the bladder is favored, if not caused, by the presence of bacteria. It is well known that in chronic vesical inflammation phosphatic calculi frequently occur, and are usually attributed to changes in the reaction of the urine induced by the bacteria. Often the stones are multiple, and by attrition wear smooth surfaces (facets) at the points of contact. The nuclei of most calculi consist of a colloid containing uric acid. When the stone is composed entirely of this substance, it is yellow or reddish-brown and the surface irregular. On section stratification is usually evident, particularly in the larger stones. When composed of calcium oxalate the calculus is hard, sometimes spiculated, and the surface formed of small bosses (*mulberry calculus*). The phosphatic calculi are composed of triple phosphates and usually contain urate of ammonium and calcium carbonate. Occasionally the stone consists of calcium carbonate alone. Cystin, xanthin, and cholesterin calculi are rare; a few cases of indigo calculus have been reported. Vesical lithiasis is commonly attended by cystitis, which in some cases is marked. Hematuria is frequently present.

Tuberculosis of the bladder may be a part of a wide-spread genito-urinary lesion involving the kidney, ureter, bladder, prostate, seminal vesicles, spermatic duct, epididymis, and testicle. The infection may occur from the blood, by lymphatic extension, or from contiguous esion in the prostate or seminal vesicles, or other adjacent tissues In general miliary tuberculosis, tubercles may be observed in the submucosa of the bladder; they are rarely conspicuous or abundant. The

Plate XVIII.

TUBERCULOSIS OF THE BLADDER

Drawing made from fresh specimen
One-half natural size

LABORATORIES OF THE JEFFERSON MEDICAL COLLEGE HOSPITAL

A.—Centre of large ulcer. At the end of the line is a distinct furrow, to which was attached a recent slough.
B.—Similar ulcer, but more recent.
C.—More recent ulcer almost ready to become confluent with the large ulcer.
D.D.D.—Miliary tubercles. These at first glance resembled ulcers, but close inspection showed that they had not as yet broken down. Many of these are seen, particularly at the base of the bladder.
E.E.E.E.—The point from which was excised the trigone prostate and urethra.
F.F.F.—Points showing the patchy inflammation of the mucosa, which accompanies tuberculosis of the bladder.

most frequent manifestation of vesical tuberculosis is the ulcerative form, which is rarely, if ever, primary. The ulcers may be solitary or multiple; commonly there is a single large ulcer, near which are grouped numerous smaller ones which extend by coalescence. The floor of the ulcer is shaggy, dirty yellow in color, and often undulated; as a rule, the muscular layer of the bladder escapes, although Senn observes that the wall is sometimes perforated. The edges of the ulcer are usually elevated, slightly undermined, and but little indurated. Commonly the entire vesical mucosa is the seat of patchy hyperemia, which is particularly marked near the margins of the ulcer; this in part accounts for the accompanying hematuria. As a result of mixed infection the coincident cystitis is often marked, and erosions of the mucosa are frequently present. Bryson has noted the occurrence of submucous rhexis giving rise to punctate hemorrhages which are particularly abundant in the zone nearest the ulcer. Small sloughs coming from the lesion and tubercle bacilli can usually be demonstrated in the urine. (Plate XVIII.)

The microscopic examination of such ulcers renders it evident that the extension is not wholly due to the presence of tubercle bacilli. Characteristic tubercles are rarely abundant, and are more conspicuous near the margins of the ulcer than in the floor. Necrosis and disintegration rapidly invade the developing tubercle and promptly convert it into a small ulcer, which, if seated near the larger lesion, quickly becomes confluent with the latter. Many of the smaller blood-vessels are thrombosed, and I have no doubt this is a determining factor in the extension of the necrosis. Tubercle bacilli are not commonly abundant in the lesion.

Tumors of the bladder[1] are not of frequent occurrence; Gurtl, in an analysis of 16,687 tumors of all kinds, found 66 vesical neoplasms. They are twice as frequent in men as in women. The secondary tumors of the organ are the result of extension from some contiguous tissue, usually the prostate; metastasis to the bladder is rare. The most common of these neoplasms is the **papilloma,** called by Rokitansky **villous cancer,** but shown by Virchow to be primarily nonmalignant. The surface of such neoplasms is composed of long slender fimbriæ (**papilloma fimbriatum**) which, when the bladder is empty, may be caught in the urethral orifice and, by subsequent distention of the organ, pulled off, in this way wounding the slender vessels in the connective-tissue core of the papilla and producing hemorrhage, which may be fatal. Usually such masses are small, although papilloma of this type may involve the entire vesical mucosa. They are sometimes associated with the presence of calculi, to which they may be due. Occasionally such tumors become cancerous, and in that way offer some justification for the term **villous carcinoma** of the bladder. In such cases the wall of the organ is invaded by the new growth, which may also extend into contiguous tissues. As the papilloma commonly arises in the area of the trigone, the secondary cancers also occupy this region. Both the papilloma and carcinoma are usually accompanied by catarrhal cystitis, and it is possible that they may follow long-continued irritation.

[1] Lendorf, "Hospitalstende," Copenhagen, lxvii, No. 30. Freyer, "Lancet," Jan. 24, 1903, p. 215. Spooner, "Post-Graduate," Oct., 1903, p. 859. Grelinski, "Zentralbl. f. Chir.," Oct. 29, 1904. Lockwood, "Lancet," June 11, 1904, p. 1633. Wilder, "Amer. Jour. of Med. Sci.," Jan., 1905.

similar growths are produced by Bilharzia hæmatobia infection. **Scirrhous carcinoma** and **encephaloid carcinoma** of the bladder occur, they are, however, exceedingly rare. Fibroma, myxoma, and myoma are infrequent tumors of the bladder. **Primary sarcoma** of the bladder has been reported, but is infrequent; of the eighty-eight vesical neoplasms studied by Albarran, only three were sarcomata; they are always sessile and arise in the connective tissue of the bladder-wall.

The most frequent disease of the urethra is inflammation (**urethritis**), which may be acute or chronic and is usually purulent. A specific inflammation of the urethra due to gonococcus is called **gonorrhea.** (See p. 107.) After a brief period of incubation (usually a few days) the mucosa of the urethra is reddened, rapidly followed by a discharge which at first is catarrhal in type, but soon contains a sufficient number of polymorphonuclear leukocytes to justify the name purulent. The epithelium desquamates rapidly, at points exposing the membrana propria and giving rise to the intense irritation particularly during urination. In mild cases the changes of the submucosa are not marked; when the infection is severe or has persisted for some time, the polymorphonuclear leukocytes infiltrate the connective tissue and may even collect in sufficient numbers to give rise to small abscesses. Usually the inflammation stops short of actual suppuration in the submucosa. The intense swelling of the earlier stages may constitute an obstruction to the flow of urine, and is, in part at least, the cause of the so-called *spasmodic stricture* of this stage. Often, after a period of acute mucopurulent catarrh, a chronic urethral discharge continues, usually associated with the development of strictures. The latter are due to the production of fibrous tissue in the submucosa, followed by contraction. They give rise to irregularities and pockets in which the infection persists, particularly in the posterior portion of the urethra (**posterior urethritis**). The inflammation may extend to the seminal sacs, prostate, and epididymis; the bladder is frequently involved. In chronic cases, particularly when strictures are present, the ureter and pelvis of the kidney may become infected; occasionally the organism enters the blood. (See Gonococcemia, p. 109.)

Acute catarrhal urethritis, also called **simple urethritis,** or nonspecific urethritis, may result from chemic irritation, or be due to infection by bacteria other than the gonococcus. The staphylococci and sometimes virulent colon bacilli induce the inflammation. Usually this type of urethritis is less intense than that due to the gonococcus. Other types of mucous membrane inflammation occasionally involve the urethra, but rarely give rise to conspicuous lesions

CHAPTER X.

ALIMENTARY CANAL.

The **alimentary canal** consists essentially of a tube extending from the lips to the anus, with dilatation at various points for the temporary retention of food during the processes of digestion. In the different parts of the canal are glands, the secretions of which promote digestion. The largest of these glands are anatomically distinct from the alimentary tube, but physiologically they are as much a part of the canal as are the glands in the mucosa; thus, the essential and important secretions of the mouth are supplied by the salivary glands, all of which lie without the mucosa of the oral cavity; the secretion of the stomach is from glands in the lining membrane; the mucosa of the bowel yields the *succus entericus*, a product of the intestinal glands; the most important secretions, utilized in intestinal digestion, come from the pancreas and liver. As each special part of the alimentary canal deals with a material the chemistry of which differs from the contents in other regions, and as there are important modifications in the anatomy of each division, the diseases of the various areas also differ.

For convenience in study the alimentary canal is divided into the mouth (including the pharynx), esophagus, stomach, small intestine, and large intestine.

THE MOUTH.

The mucous membrane of the mouth consists of a thick layer of stratified epithelium resting upon a loose and elastic basement membrane, under which is a most abundant submucosa, containing a large quantity of loose connective tissue; this is necessary in order to enable the mucous membrane to adapt itself to the sudden changes in volume to which the mouth is constantly subjected.

Malformations of the Mouth.[1]—The mouth is developed from the branchial arches, failure in the fusion of which results in the formation of clefts. When the failure of union is restricted to the upper lip and invades the soft parts only, the condition is properly termed **harelip**; many writers include with this condition fissure of the superior maxilla immediately under the labial defect. The fissure in the lip is usually directly below the nasal orifice, and in about ninety per cent. of the cases is on one side only. When both sides are involved, the condition is called *double harelip*. As development of the alveolar process and palate is intimately connected with the union of the soft parts forming the upper lip, it is not infrequent, when defects occur in the latter, for them to extend backward and to involve the

[1] See Maclennan, "Brit. Med. Jour.," Dec. 19, 1903, p. 1580. Also Salzer, "Zeitsch. f. Heilk.," Sept., 1902. Grætzer, "Vademecum der Kinderpraxis," 1903, p. 27. Owen, "Cleft Palate and Harelip," London, 1904.

osseous structure that forms the roof of the mouth. Such a condition is called **cleft palate.** The fissure may be limited to a small niche between the incisors and canine teeth, or it may extend entirely through the hard palate, converting the nasal and oral spaces into one cavity; occasionally, the failure of union extends still further—a cleft palate becomes **cleft face.** A median fissure situated in the lower lip, and comparable in a certain way to harelip, is occasionally observed, although statements to the contrary are often made.

More or less faulty development of the arch forming the inferior maxilla may result in a cleft at the chin or in entire absence of the bone —a condition known as **agnathia.** In the four cases of agnathia studied by Kuse[1] cartilaginous structures, representing rudimentary jaws, were present. This malformation is likely to be associated with cyclopia. Closure of the fissure that enters into the formation of the mouth, when more marked than usual, gives rise to **microstoma.** Failure to close to the usual degree leads to the formation of an unusually large mouth, called **macrostoma.** Arrests in development may give rise to fistulæ, through which the mouth or pharynx communicates with the external surface by some abnormal route. Occasionally, passages which were originally complete fistulæ close at one or both ends, thereby giving rise to incomplete fistulæ or to closed cavities in which cystic dilatation may occur. As these abnormal tracts usually arise from faulty union of the branchial arches, they are called **branchial fistulæ,** or when distinct cavities are present, **branchial cysts.**[2] The wall may contain lymphoid tissue, and occasionally dilated lymph-spaces, which may become lymphangiomatous; sometimes hemangiomata are present. The complete fistulæ ordinarily extend from Rosenmüller's fossa behind the tonsil, under the digastric muscle, and open in the neighborhood of the sternocleidomastoid. The track of such fistulæ, or the cyst wall, can constitute the epithelial structure from which cancer (**branchiogenic carcinoma**) arises. The uvula may be bifid or fenestrated; Mullen[3] has recorded a supernumerary uvula. Malformations of the tongue[4] are not frequent. The organ may be bifid or cleft, and occasionally the clefts give rise to a number of lobes—the lobulated tongue. Lingual adhesions to the lip, floor of the mouth, gums, and palate are sometimes observed. The condition called **tongue-tie** or **ankyloglossia** is usually due to an abnormally short frenum, although essentially the same result may be due to adhesions. An abnormally large tongue, **macroglossia,** may be produced by hyperplasia of the connective tissue of the organ, but it is usually a manifestation of lymphangiectasis. **Macroglossia neurofibromatosa** has been described. Similar lymphangiectasis sometimes affects the lip, in which location it is called **macrocheilia.** Eisendrath[5] reports a macrocheilia due to adenomatous enlargement of the glands of the labial mucosa.

[1] "Münch. med. Woch.," May 28, 1901.

[2] See Coplin and Brick, "Phila. Med. Jour.," April 23, 1902. Germond, Thèse de Paris, 1902. König, "Arch. f. klin. Chir.," 1903, Bd. lxx, p. 1008. Hammar, "Ziegler's Beitr.," 1904, Bd. 36, p. 506. Brunet, "Volkmann's Sammlung klin. Vorträge," xii, Seri. 30, 1904.

[3] "Laryngoscope," May, 1902.

[4] Bywater, "Brit. Med. Jour.," Oct. 12, 1901. Abbott and Shattock, "Trans. Path. Soc. of London," 1903, vol. 54, p. 231. Rosenak and Feldman, "Centralbl. f. allg. Path. u. path. Anat.," Jan. 31, 1905, p. 57.

[5] "Annals of Surgery," Sept., 1904, p. 320.

Inflammation of the mouth is known as **stomatitis,**[1] and may be catarrhal, pseudomembranous, gangrenous, hemorrhagic, or suppurative.

Follicular stomatitis is an inflammatory process in which the follicles or mucous glands are the seat of the most active inflammation, with the development of vesicles, and with closure, and finally distention, of the ducts, which may terminate in coagulation necrosis of the upper layer, giving rise to small ulcers.

Ulcerative stomatitis,[2] also known as *putrid sore mouth,* occurs in weak, debilitated children, and occasionally in adults; improper feeding and failure to keep the mouth clean may cause it; chronic poisoning, such as lead, mercury, or phosphorus, may induce this condition. It occasionally shows a disposition to be contagious, and this suggests the possibility of its being due to a specific germ, which, however, has not been demonstrated, although successful inoculation on the healthy gum has been practised. Some cases of ulcerative stomatitis[3] are due to the diphtheria bacillus; in rare instances the process may be a manifestation of tuberculosis or arise as a complication of lingual or even pulmonary infection by the tubercle bacillus.

This type of oral lesion usually begins as an ulcerative process involving the gum, and is therefore sometimes termed **phagedenic gingivitis.** It spreads superficially along the gingival margin, and gives rise to loosening of the teeth, which may drop out. The ulcers rarely involve the mucosa of the tongue and cheek; the base of the ulcer often contains a grayish-white slough; the accompanying catarrhal inflammation, and decomposition of the inflammatory products and necrotic tissue, give rise to an exceedingly offensive, sickening stench, which has led to the designation, **putrid** or **fetid stomatitis.**

Foot-and-mouth disease[4] is evidently the result of infection, although its exact character has not as yet been determined. The disease is most frequent in ruminants, particularly cows, but abundant evidence has been accumulated to establish the fact that it is communicable to man. The disease is characterized by the occurrence of vesicles on the buccal mucosa, and, although less commonly, on the entire oral mucosa. The inflammation begins by evident hyperemia and considerable thickening of the corium; vesicles form in the Malpighian layer, eventually displacing the overlying corneum, which ruptures and exfoliates, giving rise to an ulcer. These ulcers may become confluent and attain a diameter of one or two centimeters. Many of them consist of simple erosions or of exfoliations secondary to eruption of the vesicle, therefore not meriting the term ulcer. During the progress of the affection in the mouth there is usually more or less fever, and in the lower animals a similar eruption appears on the feet.

Parasitic or **mycotic stomatitis,** or *thrush,* is an infection occurring most frequently in nursing children, and is due to the thrush fungus. (See p. 165.) This fungus does not seem to attack the normal mucous membrane, but becomes engrafted upon a mucosa the surface of which

[1] For morbid anatomy, morbid histology, etc., see Inflammations of Mucous Membranes, p. 546.

[2] Also see Vincent's angina, p. 173.

[3] Munro, "Boston Med. and Surg. Jour.," Dec. 13, 1900.

[4] Brush, "Jour. Amer. Med. Assoc.," June 20, 1903, p. 1701.

is eroded or irritated by improper feeding or other causes; the disease is occasionally seen in adults after or during acute febrile processes or chronic diseases. The parasite pullulates in the interstices of the epithelium and forms a membrane, usually superficial, but which sometimes extends to the basement membrane, and, by mixed infection, may lead to ulceration. The membranous spots vary in size; at first the diameter rarely exceeds four or five millimeters. The erosion is commonly white or creamy white, not easily detached, and, on microscopic examination, contains, in addition to the specific fungus, many extraneous organisms. The disease usually begins on the tongue, but may arise primarily on, or spread to, the cheek, and thence to the tonsils, palate, pharynx, and esophagus; it differs from the preceding forms of stomatitis in the presence of the germ and in the fact that it is generally associated with marked dryness of the mouth, in contradistinction to the ptyalism that commonly accompanies other forms.

Aphthous stomatitis is a disease of infancy or childhood, but is occasionally observed in adults. The clinical history, the distribution and, to a certain extent, the lesions indicate a possibly infectious cause. On the mucous membrane small papules appear; these are sometimes converted into vesicles, and later undergo a superficial necrosis, giving rise to what is sometimes incorrectly termed an ulcer. True ulceration—that is, involvement of the connective tissue—is rare. The white, yellowish-white, or grayish erosions often present slightly elevated edges, which may be hyperemic. There is usually more or less infiltration of the adjacent connective tissue, which does not, however, undergo necrosis except in very rare instances. The erosions are commonly located on the inner surface of the lip, although any part of the mouth may be involved.

Gangrenous stomatitis[1] (also known as *cancrum oris* and *noma*) usually begins as a gangrenous process attacking the gums or cheeks, attended by sloughing in the structures involved. The soft parts and bones may become gangrenous and slough to such an extent that the greater part of the face may be destroyed by the phagedenic process. The disease usually follows some of the acute infectious processes in children; Osler states that fifty per cent. of the cases follow measles. Girls suffer more frequently than boys. The affection is most frequent between the second and the fifth year, although the cases the author has seen have been in older children—from seven to nine years old. In the beginning the affected tissues are hard and edematous, but rapidly become softer and fetid. When involving the jaw, the teeth loosen and fall out. In many instances a complicating bronchopneumonia, the lesions of which may become gangrenous, terminates the case; death may also result from septicemic or toxemic complications, and in rare cases the fatal issue is hastened by depleting hemorrhages. The infrequency of bleeding is attributable to the extensive thrombosis of the vessels in the affected area. Trambusti has shown that the lesion

[1] Ness, "Edinburgh Med. Jour.," June, 1899. Strauwen, "Gaz. Heb. de Méd. et de Chir.," Aug. 22, 1901. Sailer, "Proc. Phila. Co. Med. Soc.," Nov., 1901, p. 301. Trambusti, "R. Accad. med. di Palermo," Dec. 21, 1901, also "Il Policlin.," Jan., 1902. Fischer, "Amer. Jour. of Med. Sci.," April, 1902. Korsch, "Bolnit. Gaz. Bot.," 1902, No. 24. Oberwarth, "Deut. med. Woch.," April 23, 1903. Hofmann and Küster, "Berl. klin. Woch.," Oct. 24, 1904. See also Noma, and bibliography, p. 256.

is a progressing necrosis. All attempts to establish a specific etiology for noma have been unproductive. The organisms described by Lingard, Trambusti, Perthes, von Ranke, and others, and also pyococci typhoid bacillus, diphtheria bacillus, and other bacteria occur.

Gonorrheal stomatitis[1] sometimes occurs in adults and has been observed in the newborn and nurslings. It is manifested by a catarrhal or mucopurulent inflammation involving particularly the mucosa of the gums and cheek; sometimes a dirty gray coating resembling pseudo membrane is formed. Superficial erosions and even deeper ulceration are occasionally observed.

FIG. 337.—NOMA.

Fatal case. Infection followed measles, was distinctly symmetric, and without clear peripheral demarcation. Inoculations developed an organism resembling the Bacillus diphtheriæ; spreads containing the symbiotic organisms of Vincent (p. 174). Case reported by Prof. Rosenberger.

Pseudomembranous stomatitis is usually due to the diphtheria bacillus, but occasionally results from infection by streptococci, staphylococci, the spirillum of Vincent, and pneumococci; it is a recognized complication of pneumonia and diphtheria.[2]

Tuberculous stomatitis is almost invariably secondary to infection of the air-passages, particularly the lungs. In the case reported by

[1] Jürgens, "Berl. klin. Woch.," June 13, 1904.
[2] Frazier, "Med. Times," Dec., 1903.

Walter the infection began in the socket of an extracted tooth. Perforation of the palate may be due to tuberculous ulceration of the vault of the mouth, but is usually of syphilitic origin.

Syphilis of the mouth,[1] in the tertiary stage of the disease, usually attacks the tongue. The initial lesion affects the lip more frequently than any other part of the oral cavity. Of the 207 extragenital chancres collected by Neumann, 106 were on the lips.[1] The histology of the lesion in this location is essentially the same as in chancres occurring elsewhere. **Mucous patches** (see p. 179) may occur on almost any part of the buccal mucosa, but are commonest on the lips and palate. In the tertiary stage of syphilis **gumma** involves the mucosa or submucosa or may occur in the deeper tissues, particularly of the tongue. The ulcerations of the mouth accompanying tertiary syphilis may be differentiated from tuberculosis by the demonstration of tubercle bacilli and the presence of histologic tubercles in the lesion.

Oral sepsis[2] should include the various inflammatory conditions affecting the mouth and attended by manifest infection. Hunter believes that, in addition to the purely local influence exerted by septic processes involving the oral mucosa and gums (gingivitis) important secondary manifestations are not infrequent. Alveolar abscess, periosteitis, suppurative inflammations of the antrum and nasal sinuses, tonsils, pharynx, and middle ear, may be secondary to lesions primary in the buccal mucosa. Local infection traveling by the lymphatics may implicate the submaxillary and anterior cervical lymph-nodes. Inflammations of the gastro-intestinal mucosa may be caused by pyogenic organisms which are primarily colonized in the mouth. Hematogenous infection, manifested by pleurisy and other forms of serositis, and even ulcerative endocarditis, may have a similar origin. Hunter's contention that pernicious anemia is a sequence of oral sepsis has not been generally accepted. A form of alveolar inflammation, characterized by suppuration extending deeply into the sockets of the teeth, and called **pyorrhea** or **pyorrhœa alveolaris,** and by Arkövy, caries alveolaris specifica, sometimes induces an acute suppurative inflammation in, or chronic rarefying osteitis of, the contiguous bone.

Glossitis, or inflammation of the tongue, is sometimes the result of an extending stomatitis or arises in, and remains restricted entirely to, the tongue. The inflammations involving the surface of the organ are usually of the catarrhal type. The thickness of the epithelial layers of the lingual mucous membrane, with the irregularity of the papillæ, gives rise to a tendency to accumulation of cells that elsewhere would readily desquamate. The inflammation may be *acute* or *chronic*, *diffuse* or *circumscribed*, *superficial* or *deep*. The circumscribed form is usually dependent upon an irritant that directly affects the area involved. Such irritation may be produced by the sharp edge of a tooth, an ill-fitting dental plate, the pressure of a pipe-stem, or the injury resulting from long-continued flow of hot smoke against some part of the tongue. Sometimes the local inflammatory condition gives rise to considerable thickening of the mucosa, the thickened membrane becoming white

[1] See Morbid Anatomy of Syphilis, and also bibliography, pp. 174 and 177.
[2] See papers by Hunter, Goadby, Godlee, and discussion by a number of observers in the "Brit. Med. Jour.," Nov. 19, 1904, pp. 1358 to 1372.

or bluish-white in color; the condition is commonly restricted to a small area, to which is applied the term "smoker's patch," or **leukoplakia.**[1] Bockhart has seen sixty cases of buccolingual leukoplakia; all the patients were men, all smoked, and all were syphilitics. Gaucher maintains that ninety per cent. to ninety-five per cent. of the patients have syphilis.

Pseudomembranous glossitis and gangrenous inflammation of the tongue are rare. Harrington[2] reported an instance of membranous glossitis that gave rise to an exfoliated cast of the tongue. The diphtheria bacillus, streptococci, and occasionally pneumococci, sometimes produce local exfoliations that resemble pseudomembrane.

Inflammation of the tongue sometimes begins in the connective tissue, or the interstitial structures are involved secondarily to superficial inflammation; the condition has received the name **interstitial glossitis.** The process may be chronic and associated with the production of an excess of connective tissue, or it may be an acute suppurative lesion, which in turn is sometimes diffuse, or occasionally accurately circumscribed, giving rise to what is called **lingual abscess.**

Nigrities linguæ,[3] *parasitic glossitis*, *glossophygia*, or *black tongue* is an affection of the tongue characterized by a blackish, brownish-black, or yellowish coating developing near the median line and becoming less intense as the margins of the organ are approached. In one reported case the whole surface of the tongue was involved. A hairy appearance is sometimes produced by prolongation and thickening of the epithelium of the filiform papillæ. A number of microorganisms have been observed in the lesions, but it is not known that the condition is specific. The affection is usually unattended by important symptoms.

Riga's disease,[4] or **sublingual growth in infants,** is characterized by an ulcerative or pseudomembranous lesion, on the under surface of the tongue and involving the frenum. The process may be pseudomembranous or ulcerative, is probably of infectious origin, and due, in part, at least, to injury of the affected tissues by the lower incisor teeth. The condition occurs in nursing infants particularly, and appears as an ulcerative or necrotic process in the area indicated, followed by a granulomatous growth, which, in some cases, resembles a papilloma or fibroma. Evidently the new growth is of inflammatory origin and probably may be produced by a number of causes.

Ludwig's angina,[5] *acute infectious submaxillary angina*, *diffuse submaxillary cellulitis*, and *diffuse suppuration of the floor of the mouth* are names given to a septic process involving the tissues beneath the tongue and jaw and often extending to the structures around the

[1] Bockhart, "Monatsch. f. prakt. Derm.," Feb. to May, 1902, No. 4. Grancher, "La Presse Méd.," July 8, 1903, p. 493.

[2] "Toronto Clin. Soc.," May 7, 1902; "Jour. Amer. Med. Assoc.," May 24, 1902.

[3] Johnston, "N. Y. Med. Jour.," July 18, 1903, p. 126.

[4] Audard, "Rev. Mens. des Mal. de l'Enfance," Feb., 1902. Amberg, "Amer. Jour. of the Med. Sci.," Aug., 1903, p. 257. See also papers in "Deutsch. Arch. f. Kinderheilk.," 1904, xl.

[5] Munro, "Boston Med. and Surg. Jour.," Dec. 13, 1900. de Santi, "Royal Med. and Chir. Soc.," Feb. 10, 1903; "Brit. Med. Jour.," Feb. 14, 1903, p. 369. Hamann, "Wisconsin Med. Jour.," March 1903, p. 169. Robertson, "Amer. Med.," Dec. 28, 1901. Semon, "Brooklyn Med. Jour.," Jan., 1905. Merkel, "Centralbl. f. Chir.," 1904, xxxi, No. 48.

larynx and pharynx and sometimes into the cellular tissues of the neck. It is probably closely related to, if not identical with, the **woody phlegmon of the neck** described by the French writers. The tissues of the floor of the mouth become indurated, the tongue is forced upward and backward, and a brawny swelling occupies the submaxillary space, sometimes extending to or beyond the sternocleidomastoid muscle, and, though rarely, downward to the clavicle. Hamann has re-

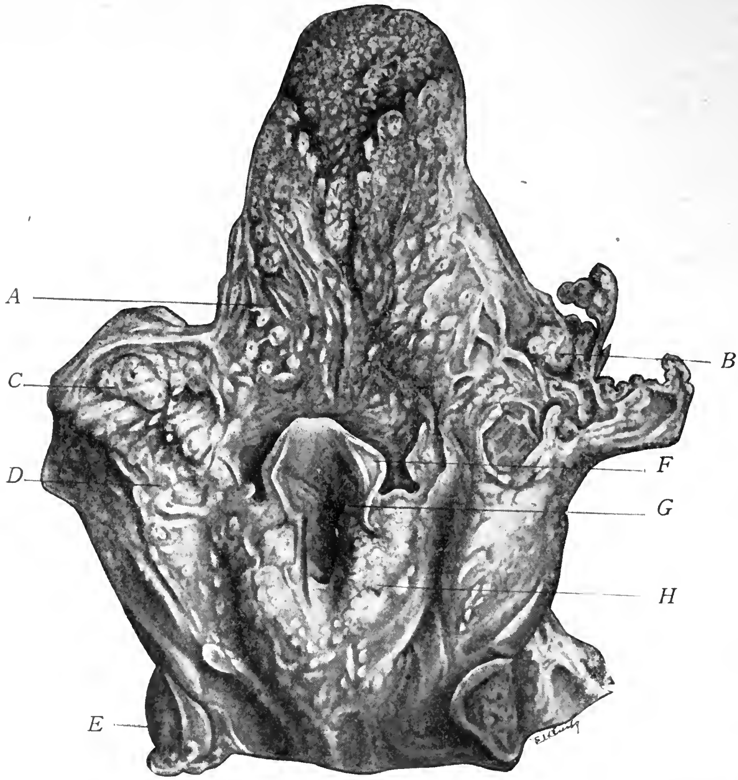


FIG. 338.—TONGUE, PHARYNX, EPIGLOTTIS, ETC., FROM CASE OF LUDWIG'S ANGINA DUE TO THE PNEUMOCOCCUS
A. Upper margin of ulcerated lingual lymph-node (lingual tonsil). *B*. Lymph-node at base of anterior arch; this node is eroded and almost dissected out by the necrotic process. *C*. Necrotic tonsil; the surface shows depressions resulting from necrosis of follicles; the corresponding tonsil on the opposite side has been cast off *D*. Ulcer in the mucosa; just below this are two prominent follicles. *E*. One-half of ulcerating pharyngeal tonsil. The other half can be seen on the other side. *F*. Free margin of the swollen and necrotic epiglottis. The leader from letter *F* runs directly into the ulcer on one side. *G*. Glottis and upper part of larynx containing corrugated masses of pseudomembrane. *H*. Similar membrane on the anterior pharyngeal wall

ported a case in which the infection resulted from pyorrhœa alveolaris. Semon regards Ludwig's angina, abscess of the pharynx, erysipelas of the pharynx, and edema of the larynx, as closely allied manifestations of infection by a number of bacteria. The organisms commonly found are streptococci, pneumococci, staphylococci, and less frequently other pyogenic bacteria. Infection usually occurs from ulcers, necroses, and injuries in the floor of the mouth or in the pharynx. In the case re-

ported by Aldrich the primary lesion involved the frenum of the tongue. Microscopic examination of the affected tissue shows a widely distributed edema, often some fibrin, and extensive infiltration by polymorphonuclear leukocytes. Collections of pus amounting to abscesses are usually absent. Pseudomembranous and necrotic processes involving the tonsils, pharynx, and larynx may accompany the condition.

The tonsils are so situated that they are particularly exposed to infection;[1] they also possess a structure that specially adapts them to the entrance of bacteria. The histologic demonstration that the surface is not uniformly covered by epithelium, and that bacteria may traverse the tonsil without giving rise to important structural alterations in the organ, render it evident why infection of the tonsil is frequently manifested by lesions elsewhere than in the organ.

Tonsillitis, also called **amygdalitis,** is an inflammation of the tonsil. It may be acute or chronic, superficial or deep; the latter is sometimes called **parenchymatous tonsillitis.** An inflammation of the contiguous connective tissue, frequently involving the tonsil, is known as **peritonsillitis,** and is usually suppurative.

Acute tonsillitis may result from infection by a number of bacteria; it may be the only conspicuous local symptom of infection by the diphtheria bacillus and also results from the local action of streptococci, staphylococci, or pneumococci. Darieu[2] states that three per cent. of the cases are due to the pneumococcus. The tonsillar enlargements accompanying influenza are probably induced by the Pfeiffer bacillus (Kamen). Tonsillar inflammation may be due to the spirillum of Vincent (see p. 173). The bacteriology of the condition indicates, and a clinical study of cases shows, that the affection is often contagious. Those afflicted by rheumatism or gout seem particularly susceptible to the condition. In scarlet fever, measles, smallpox, and, less frequently, typhoid, definite tonsillar swelling and sometimes fully developed tonsillitis occur. When inflamed, the tonsil is red, swollen, tender, and, in the earlier stages, the surface is dry and glazed. The superficial change may be that of a catarrhal inflammation. Often the crypts are distended by a white, or creamy white, semisolid exudate, justifying the name **lacunar** or **follicular tonsillitis.**

Tonsillar abscess, *suppurative interstitial tonsillitis*, or *quinsy* is an acute inflammation of the tonsil attended by the formation of pus in the interior of the organ. It probably results from infection through the crypts and sometimes follows acute follicular inflammation. The suppuration may arise in, or extend to, the peritonsillar tissue, and occasionally involves the submucosa of the contiguous pharynx. Catarrhal and also follicular tonsillitis is commonly bilateral; the suppurative or phlegmonous lesion rarely involves both sides simultaneously.

Chronic tonsillitis is characterized by an inflammation of slight intensity extending over a long period. In some cases the follicles are

[1] Hoche, "Revue Méd. l'Œst," Oct. 1, 1902. Kamen, "Centralbl. f. Bakt.," Nov. 30, 1903, p. 150. Wood, "Univ. of Penna. Med. Bull.," Oct., 1904. Gurich, "Münch. med. Woch.," Nov. 22, 1904, p. 2089. Wright, "Med. News," March 4, 1905, p. 385. Fredrick, "California State Jour. of Med.," 1905, iii, 43, No. 2. See also p. 91, and Ingestion Tuberculosis, p. 149.

[2] Thèse de Lyon, 1902.

particularly involved and the parenchyma but slightly altered; this form is called **chronic lacunar tonsillitis.** The **chronic interstitial tonsillitis** may be hyperplastic or fibroid. The former is attended by notable increase in the lymphoid tissue of the organ, and proliferation of the endothelial cells lining the lymph-sinuses. The resulting structure is soft and histologically identical with postnasal adenoids, described on p. 567. In other cases the conspicuous alteration is an increase in the fibrous tissue, rendering the tonsil firm and later, by contraction, atrophied. This condition may come on insidiously or follow the hyperplastic form.

Tuberculosis of the tonsil[1] probably occurs more frequently than the clinical studies indicate. Friedmann, in an examination of 145 cases, found the tonsil tuberculous in 17, of which 12 were primary. The affected tonsil may be of normal size and frequently the histologic lesions of tuberculosis are absent. In such cases the diagnosis rests upon the demonstration of tubercle bacilli, preferably by animal inoculation. Koplik believes that whenever the cervical lymph-nodes are the seat of tuberculosis, without evidence of general infection, we may safely conclude that the bacillus entered through the tonsil.

Actinomycosis of the tonsil[2] is exceedingly rare. Cheattie and Emery state that the instance they report is probably the second authentic case.

Pharyngitis, or inflammation of the pharynx, also called **angina,** results from infection by a number of organisms and accompanies the infectious diseases in which throat lesions are common. It may be due to the diphtheria bacillus, pneumococcus, streptococcus, spirillum of Vincent, and occasionally Friedländer's bacillus. According to Cionnini,[3] there are twenty-four recorded cases due to the pneumobacillus. There are a number of predisposing causes influential in the production of pharyngeal inflammation. These include exposure to cold, chilling, irritation by tobacco, and the inhalation of irritating fumes. Pharyngeal inflammation is said to be particularly frequent in the gouty and rheumatic, and in patients afflicted by chronic renal inflammation. The chronic forms are especially common among alcoholics, who are also abnormally susceptible to acute attacks. Several forms[4] of the affection are recognized.

Acute catarrhal pharyngitis is manifested by redness, dryness, and swelling of the mucous membrane, followed by a catarrhal exudate. Cellular infiltration of the submucosa is frequently marked. The palatine arches and the uvula usually participate in the process. After a few days the mucosa is bathed in an inflammatory exudate, the epithelium desquamated, and the submucous vessels conspicuous. The condition may be prolonged in the subacute form, or repeated attacks may lead to chronic pharyngitis.

Chronic pharyngitis, also called **chronic pharyngeal catarrh,** frequently follows the acute, particularly when the constitutional con-

[1] Glas, "Wien. klin. Woch.," 1903, No. 36. Koplik, "Amer. Jour. of Med. Sci.," Nov., 1903, p. 816. Kingsford, "Lancet," Jan. 9, 1904, p. 89.

[2] Cheattie and Emery, "Laryngological Soc. of London," Nov. 4, 1904; "Lancet," Nov. 19, 1904, p. 1426. Thevenot, "Gaz. des Hôp.," Nov. 27, 1904.

[3] "Rif. Med.," June 17, 1903.

[4] See Inflammations of Mucous Membranes, p. 546.

ditions mentioned above, favor prolongation of the affection. In childhood and adolescence the condition is commonly a manifestation of adenoids (see p. 567). Pharyngeal catarrh is sometimes associated with chronic tonsillar inflammation and generally accompanies post-nasal catarrh. The surface of the mucosa is spotted here and there by an accumulation of thick, grayish mucus. The reddening may not be marked, although in some cases the hyperemia persists. Cellular infiltration of the submucosa, and proliferation of the lymphoid tissue, may greatly thicken the membrane, giving rise to the condition called **hyperplastic** or **hypertrophic pharyngitis.** The atrophic form, also known as **pharyngitis sicca,** is often a later stage of the preceding or may arise independently. The mucous membrane is usually not so intensely hyperemic, is dry, and often appears wasted. The discharge is more tenacious, and adheres closely to the mucosa. Granular areas containing hyperplastic lymphoid tissue are sometimes present.

Pseudomembranous pharyngitis is usually diphtheric, but may be produced by any of the organisms mentioned above. In many cases the membrane formation is primary in the pharynx; in other instances it develops from extension, the lesions beginning on the tonsils, or less commonly, on the buccal mucosa.

Phlegmonous pharyngitis may be diffuse or circumscribed; the former is an infection of the submucosa which gives rise to an extensive infiltration by polymorphonuclear leukocytes. The structural changes occurring in the submucosa are essentially similar to the interstitial alterations of the connective tissue observed in Ludwig's angina. The circumscribed form of the lesion is called **pharyngeal abscess** and is usually located between the mucosa and the vertebræ. It is said to be more frequent in the rickety and tuberculous, and in the debilitated; it may be secondary to vertebral disease or follow nonsuppurative pharyngeal inflammations. Semon states that it may be produced by blows or injuries, and probably results from suppurative inflammation of the submucous lymphoid tissue.

Pharyngomycosis leptothricia[1] is a rare affection of the pharyngeal mucous membrane.

Tuberculosis of the pharynx may be acute or chronic, primary or secondary. But few cases of the primary form have been reported. In an occasional case of acute miliary tuberculosis tubercles can be detected in the pharynx and uvula. The usual form of pharyngeal tuberculosis is a chronic ulcerative process, attended by the formation of nodular granulations and ulcers, and is secondary to pulmonary infection.

Syphilis of the pharynx may be characterized by more or less specific lesions of the disease or be manifested by acute, or, more commonly, chronic, pharyngeal catarrh. Pharyngeal chancres are rare. During the secondary stage of syphilis erythematous reddening and mucous patches are not infrequently present; the latter may be bilateral and symmetric. The gumma of the tertiary period involves the posterior pharyngeal wall as a sessile induration, which may progress to softening and ulceration. The resulting ulcer is rather deep, crater-like, and possesses perpendicular edges, and sometimes an undermined margin. The floor of the ulcer frequently contains necrotic tissue and grayish,

[1] See Leptothricosis, p. 170.

mucopurulent material. Occasionally ulcers arise independently of gummata, although upon this point authorities are not agreed. The cure of such ulcers, or the cicatrization of gummata, may leave thin, grayish scars in the pharyngeal mucosa.

Diphtheria[1] is one of the most common of the grave infections involving the tonsils, pharynx, nose, and laryngeal mucosa. It may attack the lips, gums, and buccal mucosa, as well as the structures just mentioned. Of the 220 cases examined by Councilman, Mallory, and Pearce, a definite membrane was present in 127. It was on the tonsils in 65; epiglottis, in 60; larynx, in 75; trachea, in 66; pharynx, in 51; mucosa of nares, in 43; bronchi, in 42; soft palate, including uvula, in 13; esophagus, in 12; and on the tongue in 9. Burrows states that in 1528 cases of diphtheria the membrane was on both tonsils; in 243 cases on one tonsil; in 404 cases on the uvula; in 173 cases on the posterior pharyngeal wall; in 244 cases on the palate; in 12 patients the lips were involved, and in 3 the tongue. The membrane occurred in the nose in 71; the inner surface of the cheek, external auditory canal, outer canthus of eye, and vulva were each involved in one instance. It is to be remembered that infection by the Klebs-Löffler bacillus may be manifested by catarrhal, gangrenous, or pseudomembranous lesions.[2] In typic cases there is a marked hyperemia, followed by exudate in the submucosa, which commonly produces a notable swelling. Fluid portions of this exudate, and often many leukocytes, pass through the surface, undergo necrosis, and form the membrane; the necrosis may extend into the submucosa and involve the contiguous tissues. This process gives rise to a grayish or grayish-yellow, dirty membrane, or when thicker it may be almost black. Separation of the dead tissue occasionally produces definite ulcers. In the earlier stages the margin of the necrotic tissue is indefinitely outlined, but when separation has begun, the periphery is often sharply defined. The visceral lesions of the affection will be found enumerated on page 120. Mixed infections are the rule, the concurrent bacteria being streptococci, staphylococci, and pneumococci. The glandular enlargements accompanying the disease are due to the action of toxins or the entrance of associated bacteria. **Chronic diphtheria** may result from prolongation of an acute attack, the bacillus remaining in the discharges from the affected mucosa; or, as originally pointed out by Concetti, the affection may be chronic from the beginning, at no time manifesting the virulent phenomena of typic acute diphtheria. In these cases the pharynx or nasal mucosa is slightly reddened, and pseudomembrane formation is inconspicuous or absent. In Neufeld's case virulent bacilli were present for five months. Symptoms of systemic intoxication are usually absent. The late Dr. Packard referred to such cases as *bacteriologic diphtheria*, distinguishing them from the more evident forms, which he called *clinical diphtheria*. Pavlovski[3] proposes for this form of infection the name *diphtheromycosis*. A small percentage of cases of chronic follicular tonsillitis belong with this group.

[1] See p. 118. Also Councilman, Mallory, and Pearce, "A Study of the Bacteriology and Pathology of Two Hundred and Twenty Fatal Cases of Diphtheria," 1900. Pearce, "Proceed. Path. Soc. of Phila.," June, 1901. Neufeld, "Deut. med. Woch.," May 12, 1904. Burrows, "Amer. Jour. of Med. Sci.," Feb., 1901.

[2] See Inflammation of Mucous Membrane, p. 546.

[3] "Roussky Vratch," Jan. 29, 1903.

Under the name **diphtheroid angina**[1] or **pseudodiphtheric angina** are included a number of conditions clinically and anatomically resembling diphtheria, but due to causes other than the Klebs-Löffler bacillus. Hill found that in 1251 cases, clinically diagnosed diphtheria, cultures from 37.25 per cent. did not yield the diphtheria bacillus. Less than half of the cases examined by Michelazzi contained the Klebs-Löffler bacillus. The organisms producing this condition are pneumococci, streptococci, staphylococci, bacillus of Friedländer, and, less commonly, other organisms. The lesions in many cases can not be differentiated from those depending upon the diphtheria bacillus. The systemic phenomena are usually less marked, but even this criterion is untrustworthy. It is probable that many, if not all, of these forms are as communicable as true diphtheria.

Tumors of the Mouth and Pharynx.[2]—An interesting abnormality is sometimes seen at the base of the tongue at or near the point where the thyroglossal duct once opened. This consists of a tumor-like formation composed of more or less normal thyroid tissue, and is called **lingual goiter.** Its unusual position is dependent upon the fact that during fetal life the duct of the gland opened at this point, and ectopic portions of thyroid tissue, undergoing hypertrophy later in life, give rise to distinct tumors usually of the adult epithelial type. *Papillomata* occur on the tongue and cheek, rarely in the posterior part of the mouth or in the pharynx. *Adenomata* may involve the tonsil, and occasionally the pharyngeal wall; Theisen[3] has collected the cases of lipoma of the tonsil, of which six are recorded. Of the embryonic epithelial tumors, the *squamous epithelioma* is the most common; its usual seat is upon the tongue or lips, more commonly the latter; squamous epithelioma of the lip is, of all forms of cancer, the most frequent. Of the 350 cases observed by Stoker, but three occurred in women; the three females were smokers. In 4 cases the tumor was situated in the upper lip. He has not observed the condition in patients under thirty years of age. Of the 34 cases of cancer of the tongue reported by Boyd and Unwin, 27 began in some part of the organ and 7 arose in the frenum; 3 of the patients were women; the youngest was forty-two years. Hutchinson believes that in thirty per cent. of the cancers of the tongue there is a history of syphilis. Rödieger[4] states that in 30 cases of lingual cancer the first manifestation was a nodule in 14 and an ulcer in 10. Butlin and Spencer describe a form of atrophic cancer of the tongue; in one of the reported cases the right half of the tongue was completely withered and the secondary deposits also showed atrophy. Fripp and Swan have analyzed 44 recorded cases of sarcoma of the tongue, of which they think but 29 are certainly of this nature. The largest recorded specimen weighed 400 gm.; a pedunculated form of lingual sarcoma has been observed. Pharyngeal polyps and sessile tumors of the pharyngeal wall are rare. Dermoid tumors of the tongue, pharynx,

[1] Michelazzi, "Il Policlinico," Rome, 1904, No. 9. Testevin and Busquet. "La Presse Méd.," Sept. 3, 1904, p. 565. Hill, "Boston Med. and Surg. Jour.," Dec. 15, 1904. Vincent, "Lancet," May 18, 1905, p. 1260. See also ulceromembranous stomatitis, p. 173; Diplococcus pneumoniæ, p. 109; and streptococcus infections, p. 115.

[2] "The Practitioner," May, 1903, is largely devoted to tumors of the mouth.

[3] "Laryngoscope," Aug., 1903.

[4] "Beitr. z. klin. Chir.," Bd. xxi, H. 2.

and buccal floor are occasionally observed. The lymphangiectases have been described (see p. 674). Of the adult connective-tissue tumors, *lipomata*, *fibromata*, *myomata*, *chondromata*, *hemangiomata*, and *lymphangiomata* occur. The last of these occur as *macrocheilia*, or lymph lip, and *macroglossia*, or lymph tongue; these conditions are sometimes spoken of as *lymphangiectases*, or dilatations of the lymphatics in the tongue and lip respectively. Of the *sarcomata*, or embryonic connective-tissue tumors, but few occur in the mouth; myeloid sarcoma of the lower jaw is the most common form.

An **epulis** is a tumor situated on, or springing from, the gum. It may, therefore, be a papilloma, carcinoma, fibroma, sarcoma, or other tumor in that situation. In a statistical study of 118 tumors of the upper jaw Stein[1] found that 64 patients were men; forty-nine per cent. of the tumors were carcinomata and twenty per cent. sarcomata. He states that cancer usually begins in the antrum of Highmore and sarcoma in the alveolar process. Giant-cell sarcoma of the jaw is one of the frequent neoplasms involving the mouth. (See p. 354.) Reference has already been made to pharyngeal and postnasal adenoids. (See p. 567.) A neoplasm of vast surgical and clinical importance is the retropharyngeal sarcoma—a tumor springing from the submucosa or osseous structures of the pharyngeal vault. It usually attains a high degree of malignancy, and its peculiar location renders removal difficult. Endotheliomata of the pharynx and tonsil are infrequent.

SALIVARY GLANDS.

Parotitis, or **mumps,** is an infectious inflammation occurring in the parotid gland. It is, no doubt, due to some form of infection, although the exact nature of the infectious agent has not been demonstrated. A chronic infection may occur in any of the salivary glands. The parotid seems more or less susceptible to septic influences, and is not infrequently inflamed during septic diseases, and occasionally in ordinary febrile processes; the condition is referred to as **parotid bubo.** Acute inflammation of the parotid gland sometimes follows operation, particularly on the abdomen.[2]

A similar suppurative condition is sometimes observed in the sublingual and submaxillary glands. In the last two organs the suppuration may be secondary to infections of the surrounding tissues. (See Ludwig's Angina.) So far as known, the suppurative interstitial inflammations are the only examples of pure interstitial disease in its acute form affecting these organs.

Chronic Interstitial Parotitis (*Parotid Sclerosis*, *Fibroid Parotid*, *Indurative Parotitis*, *etc.*).—A study of salivary secretion made by Dickinson, who frequently catheterized the duct and showed that often the salivary output was materially below the normal, and the histologic studies made by Harris, who demonstrated the chronic fibroid changes in the salivary glands, all point to the fact that, like the pancreas, liver, and kidney, these organs are liable to chronic interstitial overgrowth comparable to that seen in the other organs just mentioned. (See Figs. 339 and 340.)

[1] "Arch. f. klin. Chir.," 1902, Bd. 65.

[2] Morley, "Amer. Gynecology," Dec., 1902. Wagner, "Wien. klin. Woch.," 1904, No. 54.

Mikulicz described a chronic symmetric enlargement of the lacrimal and parotid, and sometimes involving the sublingual glands. The parotids may be quite prominent; the condition usually shows no tendency toward suppuration, and the general nutrition of the patient is uninfluenced. Tietze has found a parasite, thought to be a protozoan, in the tissues. The condition is called Mikulicz's disease.[1]

Hypersecretion, sialorrhea, or **ptyalism** usually occurs in inflammations of the mouth, as a symptom of chronic poisoning by mercury, phosphorus, or copper, and as a physiologic result of the administrations of jaborandi and certain iodin compounds; it is also present in hydrophobia and in other diseases, both acute and chronic, primarily or secondarily involving the nervous system: *e. g.*, hysteria, trifacial neuritis, optic neuritis (?), and sometimes late in tabes. The reverse of the

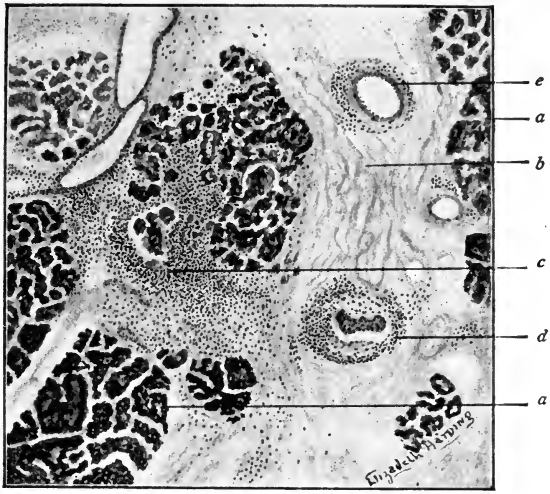


FIG. 339.—SECTION FROM RIGHT PAROTID.[2] (Carbol-toluidin-blue and eosin. Bausch and Lomb, $\frac{2}{3}$-inch Oc. B. *a*, *a*. Normal lobules. *b*. Thickened trabeculæ. *c*. Cellular infiltration into a lobule. *d*. A duct the wall of which is thickened and infiltrated with cells, and the lumen decreased in size. *e* An artery with cellular infiltration into its walls

preceding—dry mouth, aptyalism, *xerostoma*—has been observed; the exact cause, however, is not known; it is said to be a symptom of diabetes.

Sialolithiasis, or calculous disease of the salivary glands, is attended by the production of definite concretions usually situated in the ducts. The stones are chiefly composed of carbonate and phosphate of calcium, and are most common in the submaxillary glands or ducts; their localization in the latter structures is usually attributed to the large amount of mucin in the secretion of these glands, and to the fact that the mouths of the ducts are so situated that infection or foreign bodies

[1] Cheinisse, "La Sem. Méd.," Jan. 25, 1905, p. 37. Tietze, "Mittheil. a. d. Grenzgebiet. de Med. u. Chir.," xiv, No. 3.

[2] Case reported by Harris, "Boston Medical and Surgical Journal," May 18, 1899.

may enter. The calculi vary in size from the so-called salivary sand to masses 2 cm. or more in length and 1 cm. in thickness; in the case reported by Puzey the stone weighed 7.5 gm. They are commonly attended by inflammation, which may be suppurative, and sometimes perforates the cheek or floor of the mouth, giving rise to a fistula. Jarecky[1] has been able to collect 213 cases of salivary calculus. It is suggested that they are of bacterial origin, and a number examined have been found to contain microorganisms. They frequently recur after removal. The concretions resulting from infection or accumulated exfoliated cells or food-particles at the gingival margins are of a similar nature.

Obstruction to the duct of a salivary gland gives rise to a retention cyst known as a **ranula**; these are usually named after the gland involved, as *ranula submaxillaris*, *ranula retromaxillaris*, and *ranula*

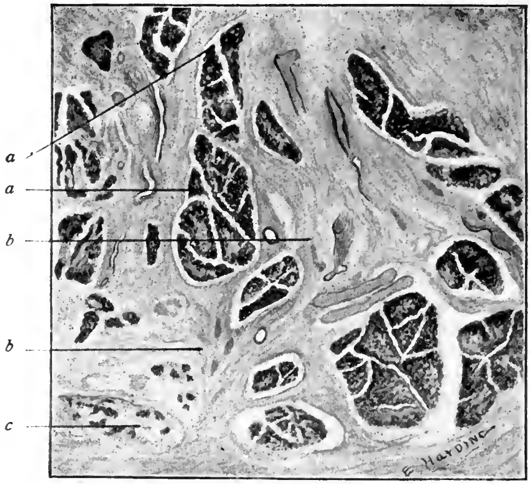


FIG. 340.—SECTION OF THE LEFT PAROTID UNDER A VERY LOW POWER.[2] (Carbol-toluidin-blue and eosin.) *a*. Normal lobules. *b*, *b*. Greatly thickened trabeculæ. *c*. Lobule almost entirely replaced by fibrous tissue The process is more recent in figure 339.

sublingualis. The classic ranula, so long considered a cyst of the duct of Wharton, is now believed to be a mucous cyst in the Blandin-Nuhn gland.

Tuberculosis of the salivary glands[3] is of infrequent occurrence. According to Fiorani, it may be diffuse or confluent, and the form observed in man corresponds to that produced by duct infection in lower animals. Of the nine cases collected by Wood, in three it was thought that the infection was by Steno's duct, one from an adjacent lymph-node, one from the blood, and in four the route of infection was undetermined.

[1] "Med. News," Feb. 18, 1905, p. 304.
[2] Case reported by Harris, "Boston Medical and Surgical Journal," May 18, 1899.
[3] Wood, "Univ. of Penna. Med. Bull.," Dec. 19, 1903. Fiorani, "Rif. Med.," Aug. 27, 1904.

Tumors of the salivary glands are not common. Of the adult epithelial type, *adenomata* occasionally occur; they are, however, exceedingly rare. Of the embryonic epithelial tissue tumors or cancers, *epitheliomata* are the most frequent, and these, histologically, are usually of the tubular variety, although squamous epithelioma has been observed. *Encephaloid* and *scirrhus* are rare. Of the adult connective-tissue tumors, *chondromata*, *fibromata*, and *myomata* occasionally occur Fibromata containing more or less glandular structure — fibroadenomata — are sometimes observed. The ordinary types of sarcoma are rarely primary in the salivary glands. The most frequent of the parotid neoplasms is the so-called mixed tumor[1] of the gland. It seems likely that more than one form of new growth has been included under this name; most of the mixed tumors are **endotheliomata.** It is possible that some of them are teratomata. They are slowly growing neoplasms that after years of indolent enlargement may suddenly develop rapidly and assume the characters of actively malignant tumors. They are usually firm, often quite hard, frequently bossed, and not uncommonly contain cysts. In the earlier stages, and often when the tumor is growing rapidly, a thick fibrous capsule may be demonstrable. Cartilage or chondroid tissue, and fibrous and myxomatous areas, are usually present. Histologically many of these tumors are typical endotheliomata, usually of the lymph-vessel type. (See p. 358.)

FIG. 341.—MIXED TUMOR OF THE PAROTID GLAND.
Weight of tumor, including contained fluid, about 3.5 kilos. The patient recovered. (Case reported by Dr. W. W. Keen, in "Jour Am. Med. Assoc.," April 30, 1904.) *A*. Large boss, upon the lower margin of which are two points of softening. *B*. Softened (necrotic) areas overlying cystic spaces.

ESOPHAGUS.

Normal Structure.—From the pharynx to the anus the essential structure of the musculomembranous tube—the alimentary canal—is that of a mucous membrane resting upon a muscular wall composed of two or more layers of unstriped muscle-fiber. The variations at different points usually consist in different glandular and epithelial layers, but the esophagus differs in its muscular layer from the re-

[1] Johnson and Lawrence, "Trans. Path. Soc. of London," 1903, vol. 54, p. 329. Wood, "Annals of Surgery," Jan. and Feb., 1904, pp. 57 and 207.

mainder of the tube, in that the upper part possesses little or no unstriated muscle, while the muscle present in the lower end is, like that in the remainder of the alimentary canal, composed exclusively of unstriped fibers. The epithelium of the esophagus is stratified throughout.

Malformations of the esophagus[1] are rare; probably not more than seventy-five instances are on record. In the larger number of cases the malformation is the result of partial absence, or failure of the two parts to fuse in a normal manner. Sometimes the upper and lower sacs are joined by a fibrous cord and there is no communication with the trachea. In another form the upper end of the lower segment opens into the trachea or into a bronchus. Congenital fistulæ in the neck, and also cysts communicating with the esophagus, are by some classed with the malformations of the organ. I have referred to them elsewhere as branchial cysts and fistulæ. (See p. 674.) Renault and Sebilleau apply the name duplication to a condition in which part of the esophagus is divided into two tubes which usually unite above and below. Congenital atresia is most frequent in the upper esophagus, and stenosis, of developmental origin, commonly affects the same area. Whipham and Fagge have been able to collect but six cases in which the lower end of the esophagus was narrowed. Sievers reports an instance of dilatation of the esophagus which he attributes to congenital defect. The demonstration, by a number of observers, and more recently by Schridde, Ruckert, and Schwalbe, of islands of gastric mucosa and glands similar to those of the cardia and pylorus in the esophageal wall, suggests an explanation for the occurrence of cysts, sometimes found in the esophagus, and also for peptic ulcers, of which Kraus has collected twenty cases in which the esophagus was involved.

Anemia of the esophagus is usually a part of general anemia. **Hyperemia** occurs in the initial stage, and accompanies inflammation of the organ. **Congestion** is marked in the venous distention of chronic heart disease and pulmonary obstruction, such as emphysema and fibroid pneumonia. A condition closely allied to congestion is **varicosity of the esophageal veins.** This is usually dependent upon venous obstruction in the liver, as observed, for example, in cirrhosis. Anastomosis between the lower esophageal veins and the veins of the stomach affords egress for the blood, which would otherwise be forced to pass through the contracting liver. Rupture of the dilated veins in the esophagus may give rise to fatal hemorrhage.

Esophagitis—inflammation of the esophagus—usually results from injury. *Catarrhal*, *hemorrhagic*, and *gangrenous* processes follow the application of corrosive substances, such as strong acids, alkalies and cauterants, mercury, salts of copper, etc.; scalds and burns induce similar changes. The severity of the process varies, and depends upon the agent used, the concentration, the length of time it acts, and the

[1] Landauer, "Centralbl. f. inn. Med.," April 22, 1899. Marsh, "Amer. Jour. of Med. Sci.," Aug., 1902, p. 304. Bickel, "Beitr. z. klin. Chir.," xliv, No. 3. Phocas, "Revue de Chir.," Nov. 10, 1903, p. 593. Thomas, "Lancet," Feb. 6, 1904, p. 361. Schaffer, "Virchow's Arch.," 1904, Bd. 177, p. 181. Renault and Sebilleau, "La Bulle. Méd.," May 25, 1904. Schwalbe, "Virchow's Arch.," 1905, Bd. 175, p. 65. Schridde, "Virchow's Arch.," 1905, Bd. 175, p. 1. Ruckert, "Virchow's Arch.," 1905, Bd. 175, p. 16. Whipham and Fagge, "Lancet," Jan. 7, 1905, p. 22. Sievers, "Deut. Zeit. f. klin. Med.," Bd. 44, p. 45 Neilson, "Trans. Chicago Path. Soc.," Feb. 8, 1904, p. 73.

age of the patient; young, tender mucous surfaces are specially prone to suffer. Ulceration usually follows, should the patient survive, and contraction of the healed ulcers causes stenosis. The catarrhal form may be due to extension from the continuous mucosa above. Pseudomembranous and gangrenous inflammations are extremely rare. *Diphtheria* rarely involves the esophagus; in Councilman, Mallory, and Pearce's 220 cases there was membrane in the esophagus in 12. In alcoholics large areas of the esophageal mucosa sometimes exfoliate. A *phlegmonous esophagitis* has been observed and may be attended by the formation of definite abscesses in the submucosa. The term *esophageal pemphigus*[1] has been applied to a form of inflammation in which definite vesicles are produced, followed by rupture and the production of red, bleeding, superficial ulcers. The contiguous epithelium is grayish and often desquamated. The condition is commonly accompanied by dysphagia, which may be mistaken for stricture. Langer[2] has reported an instance of *streptothricosis of the esophagus*. *Thrush* of the esophagus has been observed, and is usually secondary to a similar process in the mouth. *Peri-esophageal suppuration* occurs as the result of injury, diseases of adjacent structures, and pyemia.

Tuberculosis[3] **of the esophagus** is rarely primary; it is usually due to penetration of the esophageal wall by a tuberculous lesion in an adjacent lymph-node or the vertebræ. Ulcerations following necrotic processes due to poisons, and occasionally the open ulcers of syphilis and cancer, may be infected by tubercle bacilli.

Tertiary syphilis sometimes gives rise to esophageal ulceration which, on healing, produces a stricture. *Gummata* may, by infiltrating the esophageal wall, give rise to obstruction, but *syphilitic stenosis* of the esophagus is usually a sequence of cicatrization of one of the lesions just mentioned.

Actinomycosis and *leprosy* rarely give rise to any esophageal manifestation. The former may extend to the gullet from lesions in the mediastinum or vertebræ.

Acquired stenosis of the esophagus occurs in two forms:

1. **Esophagismus** (*spasmodic*, *hysteric*, or *inorganic stricture*) arises as (*a*) a manifestation of hysteria, or as (*b*) a reflex phenomenon due to excessive irritability. A tender point in the esophagus—a minute abrasion or an ulcer—is so sensitive that as soon as touched by a bolus of food, or by an instrument used for exploration, spasm ensues, and relaxes only after considerable force is continuously applied for some time. When stenosis is due to muscle contraction near the lower end of the esophagus, it is called **cardiospasm.**

2. **Organic stricture of the esophagus** is a narrowing of the tube, independent of muscular contraction, and due to disease. The narrowing may be a single annular band or the stricture may be several inches in length. There are two places in the esophagus where stricture is frequent; the upper area of election is just behind the cricoid cartilage; the lower, opposite the bifurcation of the trachea.

[1] Tamerl, "Wien. klin. Woch.," July 21, 1904.
[2] "Zeit. f. Hyg. u. Infektkrank.," 1904, Bd. 47, H. 3.
[3] Shattock, "Trans. Path. Soc. of London," 1902, vol. 53, p. 430. Shrubsall and Mullings, "Trans. Path. Soc. of London," 1903, vol. 54, p. 84. Riviere, "Brit Med. Jour.," Jan. 24, 1903, p. 193.

The *causes* may be cicatrization following injury, as that of burns scalds, or escharotics; contraction and occlusion incident to the growth of cancer; or syphilis.

There is a form of esophageal stenosis, called *simple stricture of the esophagus*, that does not seem to be properly grouped with either of the foregoing. There is much doubt as to its origin, although it has been suggested that it is a developmental defect. It is a diaphragm-like narrowing, composed of an annular fold of the mucous membrane, and usually situated near the stomach; it may be caused by cicatrization of a peptic ulcer, although it is usually held that cicatricial tissue is absent.

Stricture of the esophagus gives rise to **esophageal obstruction,** for which there are many other causes: *e. g.*, foreign bodies lodged or wedged in some part of the tube; polypoid tumors of the esophagus (rare); pressure on the esophagus by neoplasms of surrounding structures, as mediastinal sarcoma, aneurysm of aorta, swollen lymph-nodes, tuberculosis, or other disease, of the vertebræ. Pressure obstruction may occur at any point; the points of stricture obstruction have been indicated.

Acquired dilatation of the esophagus is probably always secondary to some other process. It has been known to follow spasmodic stricture. Organic stricture, or any form of obstruction, commonly leads to dilatation above the point of narrowing. The sac may be fusiform, globular, or, in rare cases, may extend in one direction, forming a diverticulum. A form of dilatation, long held to occur without obstruction, and supposed to be due to atony of the pharyngeal muscles, has been described. We are especially indebted to Mikulicz[1] for the demonstration that this type of esophageal widening, called **atonic** or **diffuse dilatation of the esophagus,** is due to contraction of the circular fibers at or near the gastric end of the gullet, a manifestation for which he coined the name cardiospasm. Rosenheim and others have maintained that a congenital weakness of the esophageal muscle is an essential predisposing factor. The dilated organ is spindle-shaped and may possess a capacity of a liter or more. Esophageal dilatation may be associated with pyloric narrowing and dilatation of the stomach.

Esophageal diverticula[2] are produced in a number of ways. It is possible that some of the forms are congenital, or at least the result of developmental defects in the musculature of the esophagus. The sacs, situated in the cervical region and communicating with the esophagus, are, in some instances at least, branchial vestiges. It is customary to recognize **pulsion diverticula,** due to pressure from within, and **traction diverticula,** resulting from contraction of adherent structures contiguous to the esophagus. It is also possible that an esophageal sac might result from cyst formation in the superficial glands[3] of the esophagus. Some additional explanation is needed for the pouches lined by distinctly cylindric epithelium. Fitz suggests that gullet pouches may

[1] "Boston Med. and Surg. Jour.," June 4, 1903, p. 608; "Deut. med Woch.," 1904, vol. xxx, p. 17. See also Tyson, Martin and Evans, "N. Y. Med. Jour.," Oct. 15, 1904, p. 731.

[2] Starck, "Die Divertikel der Speiserohre," Leipzig, 1903. Ribbert, "Virchow's Arch.," 1904, Bd. 178, p. 351. Riebold, "Virchow's Arch.," 1903, vol. 173, p. 395. Vial, Thèse de Lyon, 1904.

[3] See Hewlett, "Jour. of Exper. Med.," 1901, vol. v, No. 4.

result from irregularities in the development of a Meckel's diverticulum. The pulsion diverticulum is generally thought to be a hernia of the mucosa through a weakened or imperfect esophageal musculature. It is usually situated in the upper part of the esophagus, with which it may communicate by an oval, round, or slit-like opening in the posterior or lateral wall. The sac may be of almost any size, the maximum reported length being about 12 cm. The traction diverticulum is commonly the result of an adhesion of the esophagus to an inflamed lymph-node, which later, by contraction, gives rise to a funnel-like distention of the wall of the gullet. The lesion is usually located on the anterior surface of the esophagus near the bifurcation of the trachea. Riebold states that such diverticula are present in 3.5 per cent. of adults examined postmortem. It is possible that this form may be increased in size by pressure from within the esophagus, constituting a **traction-pulsion diverticulum.** The larger esophageal pouches occurring at the lower end of the pharynx and similar structures arising in the throat are sometimes called **pharyngoceles.**

Perforation of the esophageal wall may occur from within outward in ulceration processes, as cancer, and necroses due to lodged foreign bodies, or following other forms of injury. Extensive lacerations by exploring bougies occasionally occur. The term **esophagomalacia** has been applied to conditions in which the esophageal wall is abnormally soft and appears to rupture spontaneously. **Spontaneous rupture[1] of the esophagus** is usually observed in drinking men, and Beneke believes that, in some of these cases, excessive acidity on the part of the gastric juice and low resistance in the tissues may determine an antemortem softening of the gullet. Postmortem softening and even rupture occasionally occur. Rupture may be produced by injury; in the case reported by Whipham the man had been thrown from a horse. The esophagus is occasionally penetrated from without by abscesses or tuberculous processes affecting the lymph-nodes or vertebræ. Aneurysm of the aorta sometimes ruptures into the esophagus; malignant neoplasms of the larynx may give rise to a communication between the two tubes. Tuberculosis and syphilis of the larynx or trachea rarely penetrate the esophagus.

Tumors of the esophagus[2] are not of frequent occurrence. *Papillomata* and *adenomata* are rarely encountered. *Fibromata*, *myxomata*, *lipomata*, and *myomata* are occasionally seen; such connective-tissue neoplasms may be polypoid or sessile and sometimes attain considerable size. Rokitansky reported a smooth, lobulated fibroma of the esophagus, 17.5 cm. long and 6.25 cm. in diameter. Sarkisoff records an instance of polypoid fibroma of the esophagus that underwent necrosis and was vomited; the patient recovered. The gullet is rarely the seat of **sarcoma;** of the 175 cases of sarcoma of the alimentary tract collected by Corner and Fairbank, but 14 were esophageal growths. Such tumors are occasionally polypoid; all forms of sarcoma have been observed. The most frequent tumor of the esophagus is **carcinoma,** and the usual type is the *squamous epithelioma*. Of the fifty-four car-

[1] Whipham, "Lancet," Sept. 12, 1903, p. 749. See also Beneke, "Deut. med. Woch.," 1904, No. 41.

[2] Coplin, "Amer. Med.," May 14, 1904, pp. 773–776 Corner and Fairbank, "Practitioner," June, 1904, p. 810.

cinomata of the esophagus included in Butlin's paper, three were scirrhous, one medullary, one colloid, and the remainder squamous-cell epithelioma. The tumor may be polypoid or sessile and may or may not give rise to obstruction, although it usually lessens the caliber of the esophagus by contraction, or, less frequently, the mass is sufficiently large to obstruct. The neoplasm is sometimes restricted to a small area and in other cases involves almost the entire tube. Occasionally more than one growth is present, in which case the uppermost is evidently older and those below have usually resulted from metastasis or are grafts. Ulceration is absent in about ten per cent. of the cases. Progressing necrosis may perforate the esophageal wall and penetrate the trachea, bronchus, pleura, or pericardium. Authorities are not agreed as to the most frequent location, and this probably indicates that the tumors are fairly uniformly distributed in the different parts of the esophagus. Of the 901 cases collated by Kraus, 45 involved more than one part of the organ; 397 were in the lower third, 302 in the middle, and 158 in the upper third. In some cases malignancy is not marked; the tumor may exist for a number of years without manifesting malignancy, and especially metastasis. Rolleston states that most patients die within one year after the appearance of symptoms, that carcinoma of the upper part of the esophagus is more rapidly fatal than when the lower third is involved, and that scirrhus progresses less rapidly than the squamous-cell variety. Cylindric-cell carcinoma

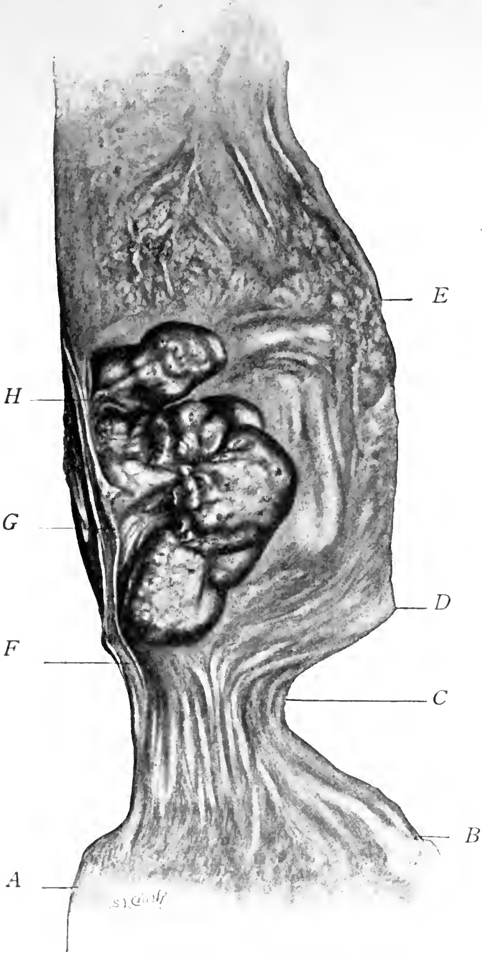


FIG. 342.—SQUAMOUS-CELL CARCINOMA OF THE ESOPHAGUS; POLYPOID TYPE.

A. Cardia of stomach. *B* to *C*. Cardia of esophagus. *C*. Hiatus esophagi. *D* to *E*. Area of maximum dilatation of the esophagus; from *E* upward the organ gradually diminishes in size *F*. Wall of esophagus. *G* to *H*. Pedicle of tumor by which are attached the projecting bosses of the new growth; at the base there appears to be but slight infiltration beneath the submucosa, although the esophageal wall is slightly thickened. The line *F*, *G*, *H*, is near the midline posteriorly from which the tumor has arisen.

of the esophagus usually occurs at or near the cardia and is generally considered with carcinoma of the stomach.

STOMACH.

Normal Structure.—The external coat is serous; the middle or muscle layer is composed of three thin lamellæ of unstriped muscle-fiber; the outer of these is directed longitudinally, the inner is arranged obliquely, while the circular fibers lie between the oblique and longitudinal. The circular fibers are most abundant near the pylorus. The muscular and serous layers are elastic, while the mucosa is less so, as a result of which, when the organ is empty, it lies in folds and elevations. The submucosa is abundant and loosely woven. The epithelium of the stomach is cylindric, but as it enters the ducts of the glands it becomes shorter and eventually cuboid. The glands are of two kinds—one predominating at the cardiac end, in structure both simple and branched, and containing columnar, cuboid, ovoid, and central cells; the other glands are most numerous near the pylorus, are also simple and branched, but differ from the preceding in that the neck or duct is longer and that the ovoid or parietal cells are absent. During life the mucosa is pink, occasionally red, but postmortem it assumes a much darker hue; this is most marked in the dependent portion, and may be mistaken for evidence of disease or injury.

Postmortem changes in the stomach result from the action of the digestive juices upon the gastric wall. In some cases postmortem digestion perforates the stomach, involves adjacent tissues, and may even penetrate the diaphragm. In medicolegal cases it is highly important to secure an early autopsy, otherwise, wounds, contusions, hemorrhages, and ruptures of the stomach can not with certainty be recognized. It is probable that during the last hours of life, particularly when the death agony is prolonged, necrotic and other changes in the gastric mucosa frequently occur. An antemortem **gastromalacia** has been described, but it is difficult, if not impossible, to say exactly how much of this softening preceded death. In embolic and suppurative affections involving the stomach the density of the tissue is often greatly lessened, and small areas sometimes undergo necrosis, but such conditions can not, with propriety, be included under the term gastromalacia.

Malposition and Malformation of the Stomach.—In the *situs inversus* and in fissural malformations of the abdominal wall or diaphragm the stomach may be transposed, or, in the latter instance, can be forced through the fissure and become more or less extra-abdominal. At birth the stomach may be lower in the abdominal cavity than is normal. Sometimes the displacement is of the stomach as a whole, and is, therefore, comparable to the acquired gastroptosis which will be described later. In other cases the dislocation is of the pyloric end only, giving rise to the so-called *vertical stomach.*

The stomach may be abnormally small, a condition called **microgastria.** When the diminutive size is the result of developmental conditions, the affection is called **primitive microgastria. Secondary microgastria** may be produced by cicatricial contraction of the organ following the action of escharotic poisons. In the case reported by Boikoff[1] the stomach was no larger than a watch. Soupault[2] has

[1] "Roussky Vratch," June 7, 1903. [2] "La Bulle. Méd.," June 28, 1902.

described a form of atrophic retraction of the stomach, greatly lessening its capacity and thought to be due to muscle spasm, resembling the spasticity observed in esophagismus. **Gastric diverticula**[1] are occasionally observed. They may be of the traction or pulsion types, and resemble similar structures occurring in the esophagus; in the stomach diverticuli are infrequent and the traction form is exceedingly rare. **Atresia** and **stenosis,** of the cardia or pylorus, are occasionally observed. Under the name of **congenital hypertrophic stenosis**[2] **of the pylorus** has been described a form of pyloric obstruction in which there is a notable increase in the muscle layer, particularly the circular fibers, and a varying degree of hyperplasia of the connective tissue in the submucosa. In the case reported by Thomson there was an increase in the submucous lymphoid tissue. There has been considerable discussion as to whether the stenosis is spastic or hyperplastic. Thomson and a number of observers hold that the spasm is primary and the hyperplasia secondary. Cautley believes that the first change is a hyperplasia or notable increase in muscle, and that the spasm is secondary. At autopsy or operation the pylorus is found greatly thickened and the lumen so narrowed that it may be impossible to force the gastric contents through the opening. When inspected from the duodenal side the pylorus often projects into the duodenum, and resembles the cervix uteri. Sometimes a longitudinal fold of the gastric mucosa occupies the opening in such a way as to indicate that the lumen has been greatly diminished after the mucous membrane developed. Microscopic examination discloses an enormous broadening in the circular muscular layer with little if any increase in the longitudinal fibers. In some cases there is an excess of fibrous tissue interspersed in the muscle. The stomach is usually dilated and in some cases the gastric walls are thickened.

Hour-glass stomach,[3] also called **bifid stomach,** and **trifid stomach,** or **multilocular stomach,** are conditions due to abnormal septa or constrictions dividing the gastric cavity into a number of smaller sacs. The most common of these is the hour-glass stomach. It is usually stated that this condition may be congenital, but Moynihan does not believe that there is a single specimen, or an authentic record, which establishes the developmental origin of the affection. He holds that all such organs are the result of cicatricial contraction of gastric ulcers, cancers, or perigastric adhesions. I have on a number of occasions, at autopsy observed a circular constriction dividing the stomach into two cavities, and giving rise to all the external appearances of an hour-glass organ, but, on closer examination, found that protracted insufflation caused the constriction to disappear. Dwight remarks that such ring-like contractions may be physiologic.

Dilated stomachs are abnormally capacious, but the increased size is due to relaxation of the muscle. The term **megastria** or **megalogastria** is applied to unusually large organs which, aside from their great size, show no abnormality. It is said that the condition is occa-

[1] Ferguson, "Glasgow Med. Jour.," March, 1898. Hirsch, "Virchow's Arch.," 1903, Bd. 174, p. 576.

[2] Moynihan, "Med. News," Oct. 24, 1903. Clogg, "Practitioner," Nov., 1904, p. 624. Scudder, "Boston Med. and Surg. Jour.," April 27, 1905, p. 494.

[3] Dwight, "Amer. Jour. of Med. Sci.," Oct., 1903, p. 581. Moynihan, "Brit. Med. Jour.," Feb. 20, 1904, p. 413.

sionally congenital, and that it is observed in those who habitually consume a diet poor in nutrients, such as the dirt- and root-eaters.

Acquired Malpositions of the Stomach.—Anterior displacements due to defects of the abdominal wall have been referred to. **Diaphragmatic hernia,** whether congenital or acquired, may permit a large part of the cardia to enter the thoracic cavity. Occasionally the hernia is through a dilated esophageal opening. Of the twenty-four congenital cases collected by Knaggs,[1] fifteen were in individuals between six weeks and sixty years of age. In nine the stomach was the only viscus that entered the sac. A number of cases of **volvulus of the stomach**[2] have been reported. It may or may not be associated with volvulus of the colon. In two of the recorded cases the torsion affected the pyloric sac of hour-glass stomachs. **Gastroptosis**[3] or **descensus ventriculi** is frequently nothing more than a part of splanchnoptosis, and rarely, if ever, occurs alone. Enlarged or dilated stomachs are particularly prone to downward displacement, but Treves and other authorities are agreed that gastroptosis may occur independently of any disease of the viscus. The essential features underlying the causes of prolapsed stomach are similar to those given for splanchnoptosis.

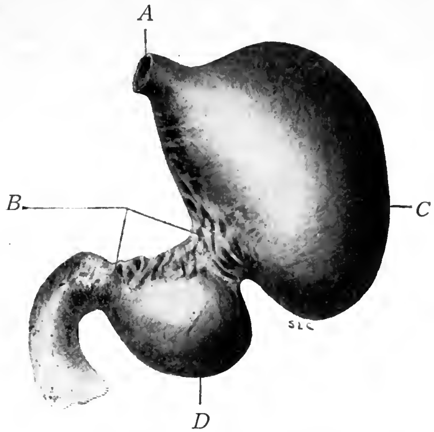


Fig. 343.—Stomach; Hour-glass Contraction Secondary to Gastric Ulcer.

A. Lower end of esophagus. *B*. The contracted and distorted part of the lesser curvature, enclosed between the two ends of the leader, marks the ulcer-bearing area. The line most distant from the letter *B* leads to the area of advanced cicatricial contraction. *C*. Cardiac complement, also called cardiac sac. *D*. Pyloric complement, also called pyloric sac.

The **bacteria of the stomach,**[4] in health, are few, and of little importance. The bactericidal action of the gastric juice, under normal conditions, exerts a distinct protective influence, and is destructive to many bacteria that otherwise might cause infection in the intestine. In diseased stomachs, and particularly in dilated organs, with or without pyloric stenosis but permitting food stasis, bacteria are particularly numerous. It was at one time hoped that the diagnosis of cancer, and possibly of some other gastric conditions, might be made by a bacteriologic examination of the gastric contents. Such expectations have not been fulfilled. At most, the bacteria indicate the reaction of the gastric secretion and rarely have any specific value in diagnosis. In the presence of hydrochloric acid, yeasts, molds, and sarcinæ are the prevailing flora of the stomach.

[1] "Lancet," Aug. 6, 1904.

[2] Spivak, "Amer. Med.," Oct. 31, 1903, p. 709. Pendl, "Wien. klin. Woch.," April 28, 1904, p. 476. Dujon, "Gaz. Méd. de Paris," March 28, 1903, p. 109.

[3] See references to Splanchnoptosis on p. 431, also Steele and Francine, "Jour. Amer. Med. Assoc.," Nov. 8, 1902, and Francine, "Univ. of Penna. Med. Bull.," Jan., 1903.

[4] See Coyon, "Flore microbienne de l'estomac," Thèse de Paris, 1900. Also Palier, "Med. Record," Nov. 19, 1904, p. 801.

Bacilli, spirilli, and cocci are usually more abundant when hydrochloric acid is absent. An organism often present is the Oppler-Boas bacillus; it is rod-shaped, 0.2 μ to 0.5 μ wide, and about 6 μ long; bent forms are frequent; the bacillus stains by Gram's method. It is a facultative anaerobe and non-motile. Kaufmann and Schlesinger found it in nineteen of twenty cases of cancer of the stomach. Palier says that it indicates deficiency in hydrochloric acid and nothing more. Infusoria[1] are sometimes found in the stomach.

Foreign Bodies in the Stomach.[2]—Various articles may be accidentally swallowed, especially by children; in other instances foreign bodies are intentionally introduced, particularly by persons attempting suicide and by the insane, or by individuals who make a living by exhibiting an ability to ingest all sorts of substances. Of the 90 cases collected by Friedenwald and Rosenthal, in 68 a single foreign body was present and in 22 they were multiple. In the case reported by Halsted there were 208 foreign bodies in the stomach; the articles present included 594 cm. (about 6 yards) of watch-chain and dog-chain, 99 nails, 88 pieces of scrap-iron of one kind or another, and 74 gm. of glass. In one reported case the stomach contained 5500 gm. (11 pounds 9 ounces) of foreign material. **Hair balls** and **string balls** result from swallowing hair or pieces of string. Masses produced in this manner may weigh 2 kilos or more and extend into the esophagus and duodenum. When small, they are usually in the pyloric area, but later mold themselves to the shape of the stomach. Ulcers of the gastric mucosa, pylorus, or upper duodenum are not infrequently present. Solid bodies frequently perforate, but often perigastric adhesions prevent escape into the peritoneum and the disastrous results of extensive infection. **Gastroliths** are extremely infrequent, and rarely weigh more than 100 gm., although in the case reported by Tidemand the weight was 1500 gm. When these or other foreign bodies remain long in the stomach, papillomata are sometimes produced.

Hyperemia of the stomach is a physiologic process during digestion, and also occurs in the initial stage of acute inflammations. The intense distention of the blood-vessels of the organ and other abdominal viscera during the chill stage of the malaria paroxysm has been variously placed, some regarding it as a visceral hyperemia, and others believing that the increased amount of blood in the viscera is the result of venous accumulation. It is not improbable that both factors are operative.

Congestion of the stomach is often marked in cardiac and pulmonary diseases associated with venous stasis, and as a result of cirrhosis of the liver; congestion may precede, accompany, or follow gastroptosis. The appearances produced by or accompanying intense congestion have been mistaken for the lesions resulting from the action of destructive or escharotic poisons.

Gastrorrhagia, or hemorrhage into the stomach, may be acute or

[1] Rosenfeld, "Deut. med. Woch.," 30 Jahrg. No. 47, p. 1717. Zabel, "Wien. klin. Woch.," Sept. 22, 1904, p. 1007.

[2] Halsted, "Contributions to the Science of Medicine," Dedicated by his Pupils to William Henry Welch, 1900, p. 1048. Friedenwald and Rosenthal, "N. Y. Med. Jour.," July 18, 1903, p. 110. Cathelin, "Bulle. et Mem. de la Soc. Anat. de Paris," Jan., 1902. Fenwick, "Brit. Med. Jour.," Nov. 29, 1902, p. 1696. Mallins, "Lancet," June 6, 1903, p. 1592. Ranzi, "Wien. klin. Woch.," Dec. 15, 1904, p. 1341.

chronic. The former may be fulminating, in which case death sometimes occurs, unattended by hematemesis or melena, although usually some blood is vomited. In acute recurring gastrorrhagia the hemorrhages are repeated at intervals which may be brief or long. In chronic gastrorrhagia a small amount of blood is continuously present; in this form the blood may not be perceptible, but can be detected by appropriate chemic tests; Boas[1] calls this **occult gastric hemorrhage.** In submucous, parenchymatous, or interstitial gastric hemorrhage, the blood escapes into the submucosa, muscular wall of the stomach, or subserosa. Blood in the cavity of the stomach usually gives rise to vomiting; when the vomited matter contains recognizable blood, the condition is called hematemesis. The altered blood is also voided in the stools, a condition termed melena.

Hematemesis may be due to increased tension within the portal vein or its branches, produced by cirrhosis of the liver, cardiac disease, or pulmonary lesions accompanied by venous stasis. Hemorrhage into the stomach also occurs in the intense hyperemia of acute inflammation involving the gastric mucosa, and less frequently in chronic gastritis. It is one of the most frequent symptoms of gastric ulcer and gastric cancer. The fulminating form is due to lesions involving larger arterial or venous branches in the stomach, or rupture of aneurysms in the gastric wall or of the splenic artery or aorta. Ruptured varicose veins may also cause gastrorrhagia. The hemorrhages produced by retching, hanging, strangulation, and epileptic seizures are rarely severe. Blows on the abdominal wall, and penetrating wounds of, or foreign bodies in, the stomach, may injure the mucosa and induce bleeding. Gastric hemorrhage may be vicarious. Blood may be vomited in a number of constitutional affections, among which should be mentioned yellow fever, malaria, purpura, smallpox, plague, and pyemia and septicemia, especially when embolic processes involve the gastric wall. Thrombosis of the gastric vessels, volvulus of the stomach, and hernias in which part of the gastric wall is strangulated, may produce bleeding, and in some of these conditions vomiting is possible. Gastric hemorrhage sometimes follows operations, particularly those involving the appendix and other abdominal structures, even when the stomach is believed to be uninjured. The bleeding resulting from fissures, superficial excoriations or erosions, and that accompanying infectious diseases, may be from a mucosa which, at operation or autopsy, shows no macroscopic lesions. Vomited blood may not have originated from gastrorrhagia. In hemoptysis, epistaxis, esophageal hemorrhage, and bleeding from other causes, the blood may be swallowed, and later appear in the vomit; nursing infants may suck blood from the mother's breast.

Vomited blood is usually clotted or contains coagula, is not red or frothy, as in hemoptysis, and the reaction is commonly acid. As a result of partial digestion it may be black, greenish, or granular, sometimes resembling coffee-grounds. When the hemorrhage is fulminating and the quantity of blood large, it does not remain in the stomach sufficiently long to be affected by the gastric juice and hence shows none of the changes just mentioned.[2] Small depleting hemorrhages

[1] "Deut. med. Woch.," Leipzig, May 16, 1901.

[2] Janowski, "Zeit. f. klin. Med.," Bd. 46, Nos. 1–4. Moynihan, "Boston Med. and Surg. Jour.," June 4, 1903, p. 611. Connell, "Med. News," Oct. 29, 1904, p. 823.

may give rise to marked anemia; or anemias, such as leukemia and pernicious anemia, occasionally produce gastric bleeding.

Degenerations and infiltrations of the gastric mucosa, unattended by inflammation, are observed in profound anemias and accompany various toxemias. Hayem[1] describes what he terms **degenerative gastritis,** occurring in such infectious diseases as pneumonia, diphtheria, and in typhoid, and in severe icterus. Similar lesions have been produced in animals by the subcutaneous injection of bacterial toxins. Granular and fatty degenerations of the epithelium occur, desquamation is rarely marked, and the hyperemia of acute inflammatory conditions is usually absent. In the degenerative changes accompanying anemia, particularly of the pernicious type, chronic Bright's disease, tuberculosis, and other debilitating conditions, the epithelium shows fatty and granular change and the mucosa is perceptibly thinned without any important increase in the connective tissue.

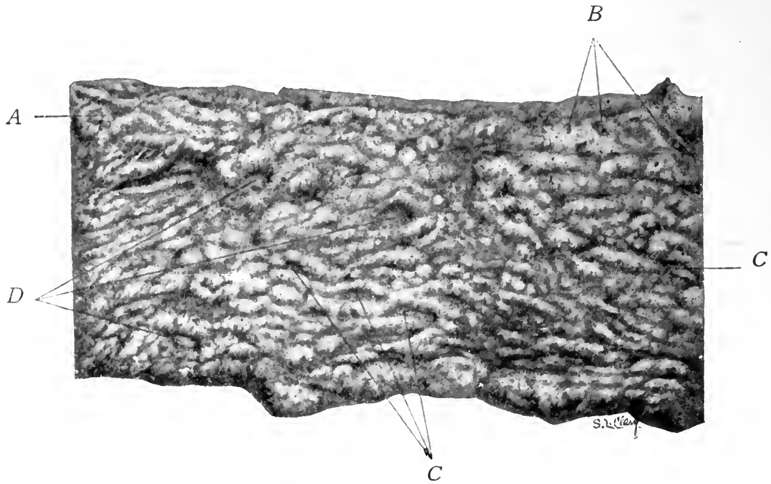


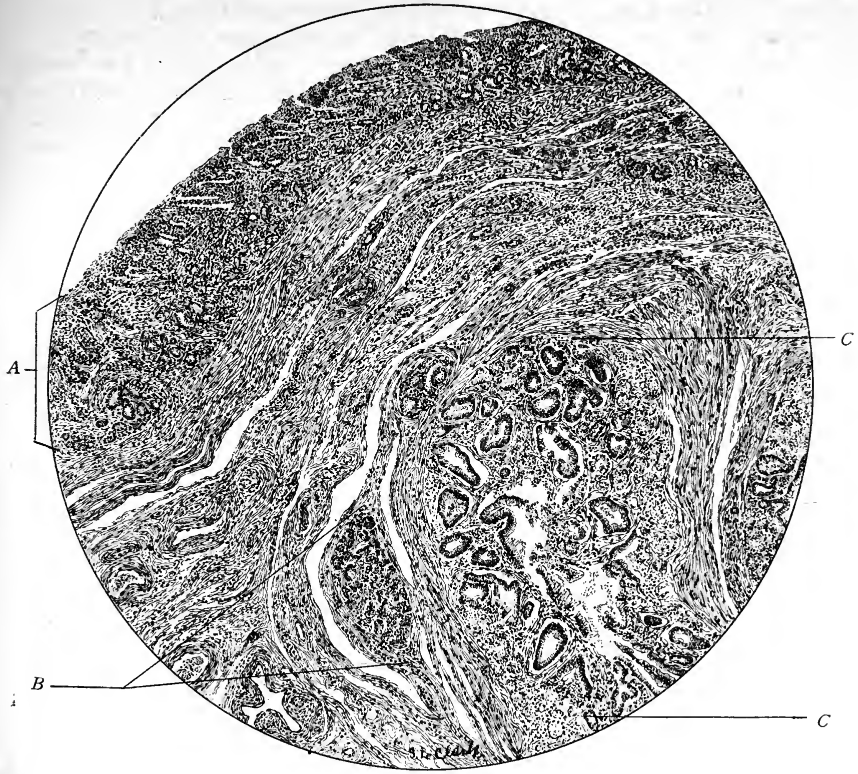
FIG. 344.—STOMACH, CHRONIC CATARRHAL GASTRITIS WITH EROSIONS. (Two-thirds natural size.) *A*. Small superficial incomplete erosion. *B*. Small erosions slightly deeper than that shown at *A*. *C*, *C*. Larger and deeper sharply circumscribed erosions. *D*. Large erosions the upper pair of which are sharply limited in part only; one margin gradually merges with the contiguous mucosa.

Gastritis is a term applied to all the inflammations involving the stomach, not including, however, the overlying serosa. When the latter structure is affected, the condition is called **perigastritis** or **perigastric peritonitis.** Perigastritis does not include inflammation of the peritoneum resulting from infection arising at some distance from, and extending to, the stomach.

Acute catarrhal gastritis, or **acute gastric catarrh,** is usually due to ingested poisons, among which should be included toxic substances, and other irritants present in the food; overeating or excessive indulgence in alcohol are also causes. There may be some doubt as to whether fermentative changes occur in a stomach the mucosa of which is normal, but all are agreed that fermentation irritates the gastric mucosa and may produce inflammation, or intensify a pre-existing

[1] "Soc. Méd. des Hôp.," Feb., 1905; "La Sem. Méd.," March 1, 1905, p. 103.

PLATE XIX.



Section of Wall of Stomach.

A. Gastric mucosa, chronic gastritis. The tubular glands are extensively destroyed and the intertubular spaces contain a notable excess of fibrous tissue, many lymphoid cells and fibroblasts. *B*. Nodule of pancreatic tissue (ectopic pancreatic lobule). *C.C*. Part of carcinomatous tissue (cylindric cell cancer) which it is thought, may have arisen from ectopic pancreatic elements.

gastritis. The affected mucosa is usually red and swollen and often coated with tenacious mucus. The submucosa frequently contains a small number of leukocytes, the epithelium is desquamating, and the vessels often distended. If the irritation has been intense, or the mucosa previously weakened, superficial erosions are occasionally present.

Chronic gastritis, also called **chronic gastric catarrh** and chronic dyspepsia, may follow a number of acute attacks or arise insidiously; it usually results from prolonged or frequent irritation, and is especially prevalent in persons addicted to intemperate eating or alcoholic excesses. The habitual consumption of highly seasoned food, sweets, and pastry may give rise to chronic gastric catarrh. Motor insufficiency and pyloric obstruction, by inducing food stasis, facilitate fermentation, which in turn irritates the mucosa and leads to chronic inflammation. Ulcer, cancer, and other morbid processes restricted to some part of the stomach, are usually accompanied by chronic gastritis.

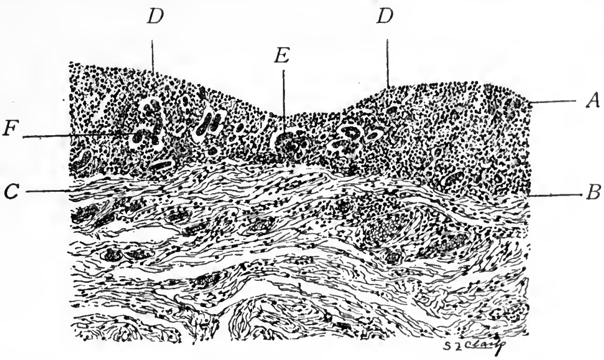


FIG. 345.—STOMACH, CHRONIC CATARRHAL GASTRITIS WITH EROSIONS; VERTICAL SECTION THROUGH AN EROSION. (B and L. ⅜ in.; Zeiss projection oc. A.)

A. Surface of mucosa. *B*. Base of mucosa. *C*. Muscularis mucosæ. *D* to *D*. Limits of erosion. *E*. Line passing through center of erosion to mass of shrunken, granular, and desquamated epithelium lying in a gland space. *F*. Altered gland epithelium. The mucosa throughout is more or less narrowed and structurally altered. The number of gland tubules is greatly diminished at all points. The glandular epithelium is granular and wasted and has retracted from the sustaining connective tissue; the types of gland cells that usually can readily be differentiated are no longer distinguishable. The intertubular spaces are universally infiltrated by lymphoid cells, some of which are present in the interstitial tissue.

tritis. Continued congestion of the organ, and constitutional affections, particularly Bright's disease, predispose to the chronic lesion or intensify it when developed. The color of the affected membrane depends upon the extent of the associated hyperemia; in the earlier stages of the process the mucosa is swollen, gray, and usually smooth. Later the swelling and thickening are less intense. Sometimes the thickening gives rise to irregular folds or distinct projections (**mammillated stomach**), and occasionally the elevated mucosa is wart-like or polypoid (**gastritis polyposa**). The projecting masses of edematous and infiltrated tissue sometimes undergo necrosis and may be vomited. During this period a notable hyperplasia of the submucosa and lymphoid tissues commonly occurs. At this time a microscopic examination reveals conspicuous mononuclear infiltration in the submucous structures and between the gastric tubules; the epithelium is desquamating, usually immature, and the distinction between the different cells lining the

tubules is no longer present. The epithelial cells are commonly loaded with mucin, in a way justifying the statement that mucoid degeneration accompanies the process. In other cases the mucosa is found thinned, distinctly fibroid, abnormally smooth and dense. The gastric tubules are wasted, the epithelium scanty, and a notable increase of the connective tissue is present between the tubules and in the submucosa. It is not certain that this form has been preceded by distinct hypertrophy, as proliferation of the connective tissue and contraction may be sufficiently rapid to prevent any manifest thickening. In this form the affection is called **fibroid** or **atrophic gastritis** and the condition is identical with the **phthisis mucosæ** of other writers. The alterations in gastric secretion are usually proportionate to the extent of the lesion.

Pseudomembranous, fibrinous, or **croupous gastritis**[1] is exceedingly rare. False membrane formation on the gastric mucosa sometimes accompanies infectious diseases, but is rare, even in diphtheria. Thomson records an instance in which a complete cast of the stomach was vomited.

Phlegmonous gastritis,[2] or **linitis suppurativa,** may be diffuse or circumscribed, primary or secondary. It is due to infection by pyogenic bacteria which may enter the submucosa from the blood-stream, from the surface, or through some pre-existing lesion, such as an erosion, gastric ulcer, or cancer. The circumscribed form usually involves the pyloric area. It may give rise to a single abscess or the suppurative foci may be small and multiple. The abscess sometimes ruptures into the stomach, and again it penetrates the peritoneum. The diffuse form may involve the whole of the stomach or be restricted to one area, usually in the pyloric end of the organ. The formation of distinct cavities containing pus does not occur; the submucosa and interstitial tissue are infiltrated by polymorphonuclear leukocytes, the epithelium desquamating or in part necrotic, and the overlying serosa sometimes inflamed. About eighty-five cases have been reported; most of the patients are alcoholics. The condition sometimes complicates puerperal and other forms of sepsis.

Plastic linitis,[3] **hyperplastic interstitial gastritis,** sclerosis of the stomach, and gastric cirrhosis, are names applied to a condition in which there is an enormous increase in the connective tissue of the gastric wall. A similar appearance is produced by carcinomatous infiltration of the stomach with the production of a large amount of fibrous tissue. In either case the wall of the organ is thickened and indurated (leather-bottle stomach). The fibrous tissue increase is not always distributed in the same structures nor uniform throughout the organ; it is usually abundant in the submucosa and sometimes dense plaques are formed beneath the serosa. Histologically, it is cellular in the earlier stages and particularly abundant about the blood-vessels.

Perigastritis may be acute or chronic; the former may be suppurative or adhesive; the chronic type is usually productive. When an ulcer or other lesion, affecting the gastric wall, slowly approaches the surface

[1] Susswein, "Wien. klin. Woch.," 1902, No. 6. Foulerton, "Lancet," April 12, 1902. Grünbaum, "Lancet," Aug. 2, 1902.

[2] Kleineberger, "Münch. med. Woch.," Aug. 4, 1903, p. 1338. Moynihan, "Med. Chronicle," Nov., 1903.

[3] Hoche, "Revue de Méd.," Nov. and Dec., 1903.

of the organ and is without virulent infection, an adhesion to some contiguous structure is produced. In this way perigastric adhesions may firmly fix the wall of the stomach to some adjacent viscus or the abdominal parietes (adhesive form of perigastritis). If the lesion be attended by pyogenic infection, the margin of the area may be walled by fibrin, which later, in favorable cases, organizes and limits the suppurative process. A distinct collection of pus is formed (**perigastric abscess**), or, in the absence of adequate adhesions, the infection extends into the peritoneum and causes general peritonitis. An extending or necrosing lesion within the stomach may, by the formation of adhesions, penetrate a contiguous organ without giving rise to general peritonitis; in this way fistulæ between the stomach and colon are produced, and in a similar manner gastric ulcer or carcinoma may extend into the spleen and liver and through the diaphragm. Chronic productive perigastritis is identical with the localized hyperplastic serositis described on page 473.

Tuberculosis of the stomach[1] is rare. Terrannini has shown that the gastric juice is not destructive to tubercle bacilli, but the experiments of Arloing indicate that the mucosa is resistant, and rarely, if ever, infected from the surface. Arloing believes that infection by the blood-stream readily occurs. A simple ulcer may become tuberculous. Of the 147 tuberculous ulcers collected by Arloing, perforation occurred in 13. The edges of the ulcer are undermined and the base commonly granular; neither bacilli nor tubercles are abundant. The case reported by Van Wart is the only instance of which I know, where the lesion was not associated with evidence of tuberculosis in other organs. The nodule was covered by the intact mucosa and contained caseous material and tubercle bacilli; several small ulcers were also present. Simmonds in 2000 autopsies on tuberculous subjects found secondary gastric ulcers in 8. Occasionally hematemesis is produced.

Syphilis of the stomach[2] occurs in both the acquired and hereditary forms of the disease. The gastric manifestations may consist of gummata which may be multiple, syphilitic ulcer of the stomach, and chronic inflammations of the mucosa. Dieulafoy also mentions hemorrhagic erosions, ecchymoses, and cicatricial contraction, the latter resulting from healed lesions. The gummata may soften and give rise to ulcers which occasionally perforate; ulcerative lesions may also result from obliterative changes in the blood-vessels of the gastric mucosa. Hemmeter and Stokes have reported a case of hypertrophic gastritis of syphilitic origin. Einhorn states that syphilis of the stomach may cause pyloric stenosis.

Gastric ulcer,[3] **peptic ulceration,** simple ulcer of the stomach, and

[1] Arloing, "Les ulcerations tuberculeuses de l'estomac," Paris, 1903. Terrannini, "Rif. Med.," June 24, 1903. Van Wart, "Johns Hopkins Hospital Bull.," Sept., 1903, p. 235.

[2] Einhorn, "Jour. Amer. Med. Assoc.," Oct. 25, 1902, p. 1051. Gross, "Münch. med. Woch.," Jan. 27, 1903, p. 157. Lafleur, "Montreal Med. Jour.," July, 1903. Hayem, "La Presse Méd.," Feb. 18, 1905, p. 105.

[3] The literature of gastric ulcer is too voluminous to be incorporated in this volume. See Nothnagel's Encyclopedia of Practical Medicine, American edition, volume on "Diseases of the Stomach," 1904, p. 543. Also Weilung and Effendi, "Deut. med. Woch.," 1904, No. 53. Dumeny, Thèse de Paris, 1903. F. and G. Gross, "Revue de Chir.," Feb. 10, 1904, p. 137. Howard, "Med. News," Oct. 8, 1904, p. 673. Moynihan, "Lancet," Feb. 11, 1905, p. 340.

round ulcer are names given to an affection most common in the stomach, but also involving the duodenum, and less frequently the lower part of the esophagus; Quénu and Duval believe that a similar ulcer occurs in the colon.

Welch observes that we know little more of the etiology of gastric ulcer than we did twenty years ago, at which time his exhaustive article on the subject appeared. The characteristic lesion seems inseparably connected with the presence of gastric juice; this is shown by the ordinary location of the affection and by the fact that peptic ulcers occur in the jejunum after gastroenterostomy; according to Mikulicz, there are fifteen recorded instances of ulceration in the jejunum following anastomoses between the stomach and this part of the intestine. Apparently some local nutritional disturbance renders the mucosa susceptible to the digestive action of the gastric juice. The exact character of this deteriorating influence is not known. It has been suggested that the mucosa may be altered by embolism, thrombosis, obliterative endarteritis, vascular spasm, spasm of the gastric wall, and injury, and that when any one, or a combination of these conditions, deprives the surface of its proper nutrition, the gastric juice digests the affected area and an ulcer results. MacCallum[1] has recently repeated the experiments of former observers on the production of gastric ulcer by embolism, and has shown that it is possible to induce lesions similar to those observed in man; he concludes, however, that the embolic theory does not explain all cases. Dumeny believes that the traumatic ulcers result from abrasions in the mucosa or from submucous hematomata and necrosis of the overlying mucous membrane. Gastric ulcers are frequently associated with anemia, but it is doubtful if the blood condition produces the ulcer; the most intense anemias are often unaccompanied by gastric ulceration. Although the hydrochloric acid is usually increased, conclusive evidence that hyperchlorhydria is not necessary to the production of gastric ulcer is clearly established by the occurrence of jejunal ulcers in operation cases in which the acidity was constantly subnormal. Duodenal ulcers sometimes follow cutaneous burns, and Devic and Chauret have recently called attention to a hemorrhagic duodenitis accompanying uremia and sometimes terminating in ulceration. Attempts to establish a bacterial origin for gastric ulcer have been unsuccessful. In Collin's series of 262 cases of duodenal ulcers, 242 were in the first part. Peptic ulcers are most frequent in females between twenty and thirty years of age, and in males between thirty and forty years.

Morbid Anatomy.—It is customary to divide the gastric ulcers into acute and chronic. Clinically several forms are recognized, the subdivision being based on the symptomatology. Cases accompanied by pain belong to the gastralgic form; when vomiting is abundant, the lesion is referred to as catarrhal; in the hemorrhagic type hematemesis is a dominant symptom; when anemia and wasting are present without gastric symptoms, the process is said to be cachectic; dyspeptic and latent forms are also recognized. The peptic ulcer is usually solitary, but may be multiple, and if many are present they are commonly grouped closely together. The ulcer may be situated in any part of the stomach, but is most frequent on the posterior wall near the lesser curvature and

[1] "Amer. Med.," Sept. 10, 1904, p. 452; bibliography.

toward the pyloric end of the organ. According to Pariser and Lindner, in 200 cases of gastric ulcer the posterior wall will be involved in 190, of which 4 will perforate; and of the 10 situated on the anterior wall, 8 will terminate in perforation. The ulcers rarely exceed 2 cm. or 3 cm. in diameter, but a single large lesion may possess a maximum length of 20 cm. and may encircle the stomach. The ulcer may be funnel-shaped, terraced, or saucer-shaped. In practically all cases the lesion in the mucosa is largest; when the muscular layer is involved, the destruction is less than in the mucosa. In rare cases the ulcers are undermined and the lesion in the mucosa small. In the acute ulcers the margins are sharp, punched-out, and on microscopic examination show very little cellular infiltration. In the chronic ulcer the margin is elevated and formed by a narrow zone of induration. Histo-

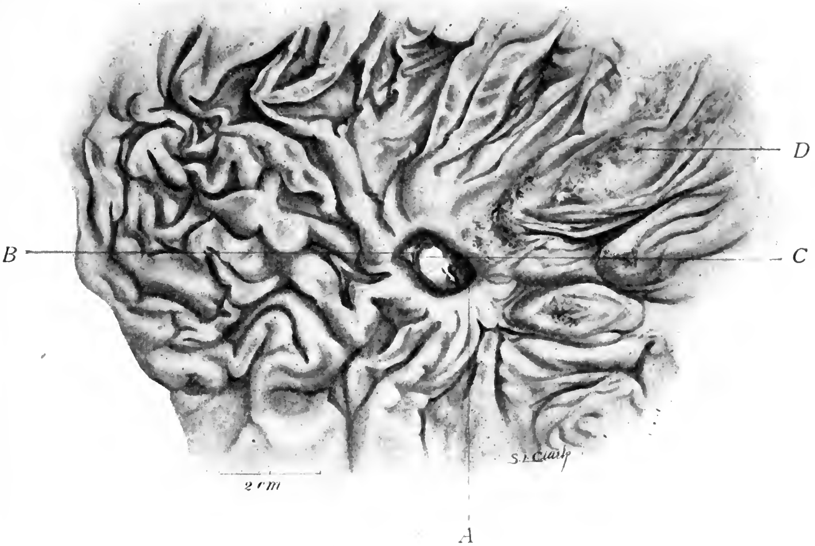


Fig. 346.—Perforated Peptic Ulcer of Stomach (Gastric Ulcer).

A. Slightly indurated margin. *B*. Exposed muscular layer, giving rise, on this side, to the appearance of a terrace. *C*. Opening extending through the serosa. *D*. Hyperemic erosions of the mucosa. (The author is indebted to Dr. A. O. J. Kelly for the specimen from which this drawing was made.)

logic examination of the indurated ring shows that it is composed of fibrous tissue and the usual cellular elements of a forming cicatrix. The floor of the ulcer may be the muscle or serous layers of the stomach, or some adjacent viscus. Peripheral adhesion and extending central necrosis may lead to perforation at some distance from the original lesion. Thue has recorded a case in which the gastric ulcer perforated the right ventricle of the heart. When adhesion to the liver or spleen occurs, an extensive necrosis may involve these organs. Robson mentions 23 possibilities that may occur in cases of gastric ulcer: (1) Local peritonitis or perigastritis with adhesions; (2) Local suppurative perigastritis; (3) Subphrenic abscess; (4) Abscess of liver, pancreas, or spleen; (5) Fistulous track between the stomach and adjoining organs

or the surface of the body; (6) Acute perforation; (7) General peritonitis; (8) Dilatation of the stomach; (9) Hematemesis and melena; (10) Tumor of the stomach or pylorus; (11) Cicatricial stenosis of pylorus; (12) Hour-glass stomach; (13) Spasm of pylorus causing intermittent narrowing; (14) Atonic motor deficiency; (15) Gastralgia; (16) Persistent vomiting; (17) Tetany; (18) Acute or chronic pancreatitis; (19) Profound anemia; (20) Pressure on or stricture of the bile-duct, causing jaundice; (21) Cholecystitis and cholelithiasis; (22) Emaciation; (23) Cancer secondary to ulcer. The frequency with which gastric ulcer is converted into gastric carcinoma has been variously estimated at from three per cent. to fourteen per cent. Mayo found a history of ulcer in sixty per cent. of his cases of cancer. In addition to pyloric stenosis it is also possible for duodenal ulcers to produce narrowing of the duodenum. In about five per cent. of all autopsies cicatrices resulting from healed ulcers can be recognized.

Pyloric obstruction may be due to **stenosis** or to occlusion by foreign bodies lodged or impacted in the opening, or pedunculated polypi may be so situated that they can be forced against or into the orifice, occluding it in a valve-like manner. Congenital hyperplastic stenosis and the narrowing incident to cicatrization of ulcers and gummata have already been considered. Cancerous tissue may obstruct the pylorus by hyperplastic thickening or by contraction. Adenoid deposits in the submucosa occasionally manifest sufficient hyperplasia to produce obstruction. Quénu and Petit have shown that pyloric stenosis frequently follows ingestion of caustic liquids; in twenty-nine such cases, when death occurred early, ten showed pyloric ulceration; and of thirty cases in which death took place after one month, in thirteen there was a definite cicatricial stenosis. The pylorus may be obstructed by conditions acting from without. It is said that in gastroptosis, unassociated with pyloric prolapse, traction on the pyloric segment of the stomach, and consequently on the pylorus, induces mechanical obstruction. Cicatricial tissue, enlarged glands, and other peripyloric conditions may cause collapse of the tube. Lotheissen[1] has been able to collate seventeen cases of duodenal stenosis due to pancreatic tumor. Neoplasms involving the bile-duct, or contiguous lymph-nodes, and tumors of the liver, sometimes obstruct the pylorus. Axhausen[2] calls attention to the pyloric stenosis produced by ecchinococcus cysts of the liver. The pressure of an enlarged gall-bladder or adhesions resulting from pericholecystitis may obstruct the pylorus. Pyloric obstruction, sufficient to be of clinical importance, is always attended by dilatation of the stomach, either acute or chronic, depending upon the rapidity with which the pylorus is obstructed.

Dilatation of the stomach[3] is defined by Riegel as a permanent enlargement of the organ combined with motor insufficiency. The condition is also called **gastric ectasy** or **gastrectasis.** While the recognition

[1] "Wien. klin. Woch.," 1903, No. 14, p. 409.
[2] "Deut. Zeit. f. Chir.," 1905, Bd. 75, p. 77.
[3] Nothnagel's Encyclopedia of Practical Medicine, American edition, volume on "Diseases of the Stomach," 1904, p. 379. Craemer, "Magenerweiterung, motorische Insufficienz und Atonie des Magens," Munich, 1903. Debove and Cardarelli, "International Clinics," 1902, vol. iii, twelfth series, p. 356. See also discussion on Dilatation of the Stomach, "Brit. Med. Assoc.," 1903; "Brit. Med. Jour.," Nov. 1, 1903, p. 1389.

of motor insufficiency is important in the chronic forms of gastric dilatation, it is clear that in some types of the acute the paralysis of the muscle is secondary to obstruction. The inadequate motor power of the stomach may cause chronic dilatation, or a gradually increasing obstruction at the pylorus, or in the duodenum, can exhaust the gastric muscle which previously was efficient. It is possible to recognize acute, subacute, and chronic forms of gastrectasis, and also types which are continuous and others in which the dilatation is intermittent.

Acute gastric dilatation, also called **acute gastrectasis,** and **gastroplegia,** or paralysis of the stomach, in most instances depends upon causes essentially identical with those producing a similar affection of the intestine, called paralysis of the intestine, **acute paralytic distention** of the intestine, **acute intestinal dilatation** or **enteroplegia.** As the pathology of these two conditions is essentially the same, I shall consider them together, following a number of observers who have adopted the term **acute gastro-intestinal dilatation.**[1] In some cases the stomach is primarily involved and suffers most; in other instances the dilatation begins in the intestine, to which it may be restricted; mixed cases also occur. The condition may result from acute obstruction, as by foreign bodies in the pylorus, volvulus of the stomach or intestine, strangulated and incarcerated hernias. There are some cases that appear to be causeless, and these have been attributed to remote nervous influences, such as neurasthenia and hysteria. The most common cause, and by far the most important, is infection, and it does not appear necessary for bacteria to be located in the peritoneum, or in the cavity of the affected organs. In such cases the paralysis depends upon the action of toxins circulating in the blood. This factor is probably productive of the gastrointestinal paralysis accompanying pneumonia, scarlet fever, and meningitis. The local influence of infection is illustrated by the intestinal, and frequently gastric dilatation, accompanying peritonitis, appendicitis, acute infections of the pelvis, cholecystitis, and other localized acute inflammatory processes involving the abdominal organs. Blows on the abdomen, and falls without gross lesion of the abdominal viscera, may be followed by gastro-intestinal dilatation. It sometimes appears after anesthesia and has been attributed to the anesthetic. Many cases follow abdominal operations, even when evidences of infection are absent. Surgeons refer to the condition as **acute paralytic ileus** or **adynamic ileus.**

Allbutt has described a subacute dilatation or atony of the stomach following infectious diseases, particularly typhoid, pneumonia, scarlet fever, and diphtheria. In these cases it is probable that the bacterial toxins have altered the muscle-fiber, or the innervation, and that, with the resumption of function, the organs manifest a tendency to dilate.

Morbid Anatomy.—At autopsy the stomach is usually greatly dilated and the walls thin and flaccid. The dilatation sometimes ends at the third part of the duodenum, where the intestine is crossed by the superior mesenteric vessels and nerves; on the other hand, it frequently

[1] Talma, "Berl. klin. Woch.," Feb. 3, 1902, p. 90. Herff, "Zeit. f. Geb. u. Gyn." (Stuttgart), xliv. Lund, "Jour. Amer. Med. Assoc.," July 11, 1903, p. 74. Reynier, "Revue de Chir.," Nov. 10, 1903, p. 593. Hoffmann, "Münch. med. Woch.," Nov. 8, 1904. Korn, "Deut. med. Woch.," xxx, Nos. 10 and 11, pp. 344 and 380.

extends into the ileum, which, with the colon, may be enormously distended. Sometimes the walls are thin, almost transparent; the serosa may be normal, but is usually drier than in health and not infrequently is the seat of beginning inflammation. The stomach usually contains more gas than liquid, and the same is true of the distended intestine. The fluid is usually thin, watery, or flocculent; it may be greenish or brownish from admixture of blood, or from bacterial growth. In autopsies made shortly after death, the mucosa sometimes weeps blood, or bloody serum. The vessels are moderately distended and erosions of the mucosa are frequently present. When punctured, the affected organs collapse without contracting. I have observed a similar condition in the bladder, and it is probable that the flaccidity of the uterus in some cases of puerperal sepsis depends upon a similar anatomic basis.

Acute dilatations of the hollow viscera, when rapid and marked, are extremely fatal; the high mortality is probably due to the intensity of the intoxication rather than to the dilatation alone. Of the thirty-four cases of acute dilatation of the stomach collected by Herff, twenty-nine of the patients died.

Chronic dilatation of the stomach, or **chronic gastrectasis,** may result from pyloric obstruction or atony of the gastric muscle. Motor insufficiency, even when unattended by pyloric obstruction, and gastroptosis, commonly gives rise to a dilated organ. All forms of slowly evolving pyloric obstruction (p. 706) increase the amount of work demanded of the propulsive forces, lead to the stagnation of food, consequent fermentation, chronic gastric catarrh, and eventually gastrectásis. It is possible that some of these cases originate in the milder form of acute dilatation. Extreme ectasy is observed in pyloric stenosis.

Morbid Anatomy.—Motor insufficiency is not characterized by any constant anatomic lesions by which it can be identified postmortem; when dilatation is present, the organ may be enormously enlarged, particularly downward and toward the left. In the beginning the enlargement is toward the left rather than downward, but later, as a result of sagging, the stomach may extend to the symphysis and nearly fill the left abdomen. When the obstruction is slight and the muscle capable of hypertrophy, some thickening of the gastric wall occurs; usually this is more marked toward the pyloric end of the organ and is an attempt to compensate for the increased resistance. When hypertrophy does not occur, or has been present and has disappeared, progressing stenosis causes wasting, and consequently the gastric wall is thin. Microscopic examination in cases belonging to the latter group discloses wasted muscle layers the cells of which may be granular or even fatty. In some instances the muscle cells are hyaline, suggesting degeneration or necrosis; the elastica is usually fragmented. The changes in the gastric mucosa are determined by the amount and character of the accompanying gastritis. Usually the mucous membrane is wasted, and the epithelium degenerated and in part desquamated; the structural alterations in the membrane are those observed in whichever form of gastritis is present. In marked cases the position of the other abdominal viscera is altered; the colon sags and may lie in the pelvis, and the liver and spleen are pushed upward and toward their respective sides by the enlarged stomach. It is alleged that in some cases the diaphragm rises, and that even the thoracic viscera may occupy abnormally high positions.

In both acute and chronic gastrectasis the secretory activity of the stomach is perverted. In the acute dilatation the gastric contents may possess no digestive action; most of the fluid present is evidently exudative in origin. It has been demonstrated that the toxicity of the liquids contained in the stomach and intestine in gastro-intestinal paralysis is higher than normal, and probably many of the symptoms are due to absorption of the contained poisons. In the chronic dilatation, fermentative changes, associated catarrhal inflammation, and distention retard digestion and absorption. Toxic substances are also generated, but the character of these bodies and their physiologic action are not fully known.

The **gastric neuroses** include a number of conditions for which no adequate explanation is afforded by any anatomic change in the stomach. Probably some cases of atony belong with this group. In many cases of *gastralgia* no structural lesion can be demonstrated; in a few instances arteriosclerosis of the gastric vessels is present. Some manifestations of hysteria, such as *rumination* or *merycism*, are included among the neuroses.

Tumors of the Stomach.[1]—Nonmalignant epithelial tumors of the stomach are rare. *Mucous polypi*, or *polyadenomata*, are occasionally observed; of the thirty-four cases collected by the Fenwicks, forty-one per cent. were solitary, and when multiple, the number present varied from 6 to 200. It is probable that some of the so-called adenomata are types of the polypoid gastritis to which I have already referred. *Papillomata* are rare. The most frequent tumor of the stomach is *carcinoma*, which may be primary or secondary; the former is the more common. The secondary growths are rarely of metastatic origin, but are usually due to extension from some contiguous viscus, such as the pancreas or biliary passages. About eighty per cent. of the gastric cancers arise in the narrow band of tissue extending from cardia to pylorus, and are usually nearer the latter orifice. The cardia is involved in about ten per cent. of the cases, and probably in some of of these the neoplasm arises in the esophagus. With regard to the morbid anatomy of gastric cancer, it is important to recognize three types of the affection: (1) The growth is fungoid, giving rise to a large projecting, cauliflower, or papillomatous mass, and manifesting little tendency to infiltrate the gastric wall. In this form ulceration is rarely conspicuous. (2) Ulcerating carcinoma produces extensive destruction of the gastric wall, and often invades contiguous structures. I have seen the ulcer penetrate the liver, in which a large cavity formed, and in another case similar extension involved the spleen and opened the splenic artery, giving rise to fatal hemorrhage. Extensive necrosis affecting the spleen, liver, or pancreas justifies the name **gangrenous cancer** used particularly by the French writers. The ulcer may be small and indurated, particularly in the scirrhous form, and often contracts, giving rise to marked pyloric stenosis. The margins of the ulcer are sometimes soft and fungoid, and in other cases extremely hard, the density depending upon the amount of fibrous tissue. Occa-

[1] Fenwick and Fenwick, "Cancer and Tumours of the Stomach," 1903. Corner and Fairbank, "Practitioner," June, 1904, p. 810. Renner, "Mitth. a. d. Grenzgebiet. d. Med. u. Chir.," Bd. xiii, H. 2, p. 113. Alessandri, "Mitth. a. d. Grenzgebiet. d. Med. u. Chir.," 1903, Bd. xii, H. 4.

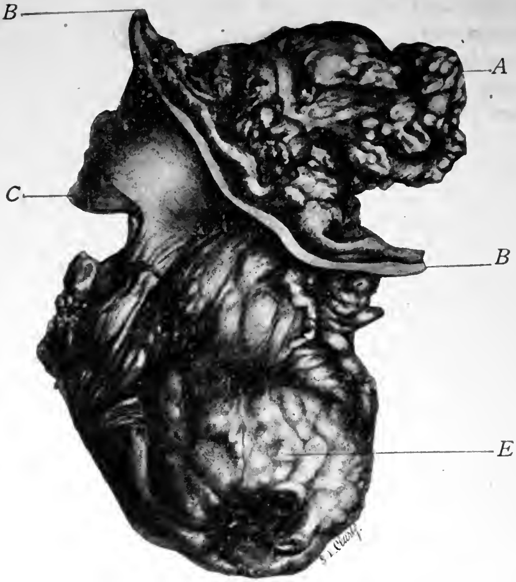


FIG 347.—STOMACH, CARCINOMA OF PYLORUS, WITH SECONDARY NODULES IN THE RETROGASTRIC GLANDS EXTERNAL SURFACE.

(Removed during life by Prof. E. E. Montgomery). A sectional view of this tumor is shown in Fig. 348. *A* Polypoid growth projecting into stomach. *B*, *B*. Gastric end of pylorus. *C*. Duodenal end of pylorus *E*. External surface of retrogastric lymph-nodes; these were removed from behind the peritoneum.

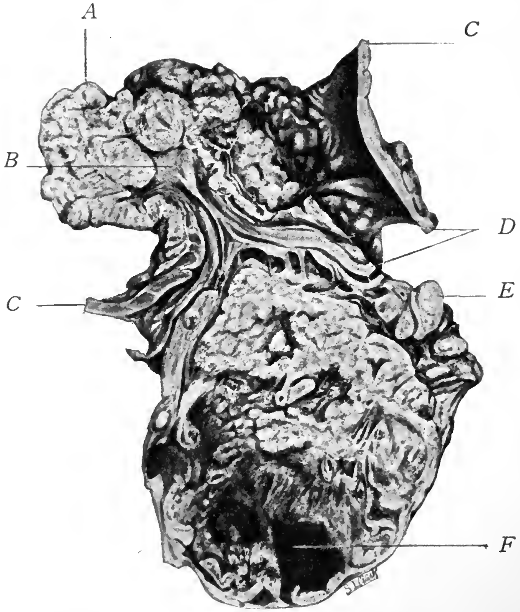


FIG. 348.—STOMACH, CARCINOMA OF PYLORUS, WITH SECONDARY NODULES IN THE RETROGASTRIC GLANDS.

Section through center of specimen; mesial surface of one-half of specimen. Removed during life by Prof. E. E Montgomery.) External surface of same mass is shown in Fig. 347. *A*. Polypoid growth projecting into stomach. *B*. Connective-tissue stalk of polypoid mass. *C*, *C*. Gastric end of pylorus. *D*. Duodenal end of pylorus. *E*. Enlarged lymph-node *F*. Necrotic area in secondary mass of neoplasm.

sionally the ulcerations are multiple. This anatomic form may encircle the stomach and is one of the causes of hour-glass contraction. In the earlier stages ulcerative carcinoma may be indistinguishable from gastric ulcer, and it is not improbable that many of these neoplasms are instances of cancerous transformation of chronic gastric ulcers. (3) This form is, in my experience, extremely rare; it is characterized by a diffuse infiltration of the gastric wall, which becomes greatly thickened and often intensely indurated (leather-bottle stomach). The capacity of the organ is greatly reduced and ulceration is inconspicuous or absent. In rare cases the diffuse induration extends to the omentum and perigastric tissues, but extensive necrosis is infrequent. In some instances of the ulcerative form diffuse infiltration of the contiguous gastric wall produces localized thickening and induration, which rarely is extensive.

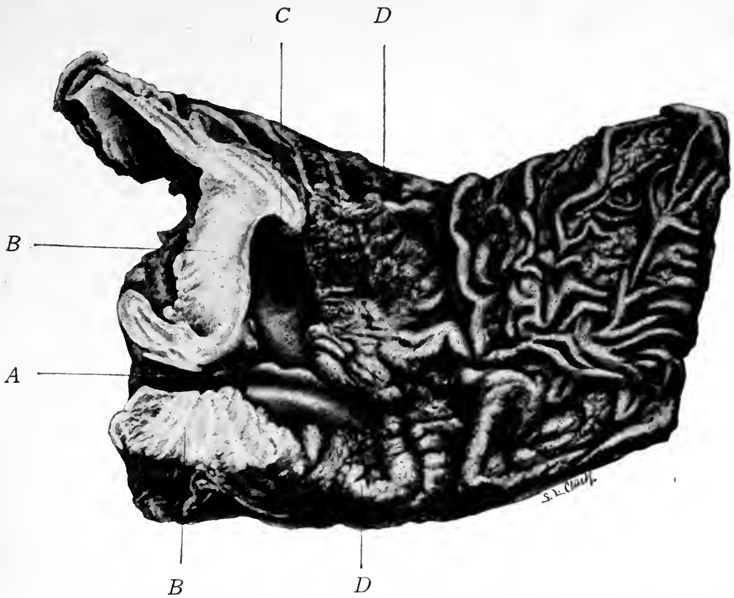


FIG. 349.—PYLORIC END OF STOMACH; MARKED STENOSIS OF PYLORUS DUE TO CONTRACTION OF SCIRRHOUS CARCINOMA.

A. Pylorus. *B, B*. Pyloric wall greatly thickened by cancerous infiltration. *C*. Smooth base of cancerous ulcer *D. D*. Gastric mucosa infiltrated by the extending cancer.

With regard to the histologic type of cancer affecting the stomach much confusion has arisen, largely due to the fact that all hard tumors were formerly called scirrhus, and the soft and fungoid masses were grouped with the encephaloid cancer. Of the 1348 cancers included in the Fenwicks' collection, 863 were encephaloid, 447 scirrhous, and 38 colloid. Of 115 specimens examined histologically, 73 were glandular carcinomata, 33 cylindric-cell epithelioma, and 9 showed signs of colloid degeneration. Cancer of the stomach is infrequent in patients under forty years of age; less than three per cent. of the patients are under thirty. The rapidity with which the lymph-nodes are involved varies in different cases. The dissemination by branches of the portal vein is common and secondary growths in the liver may be expected.

Adult connective-tissue tumors of the stomach are rare. *Myoma, fibroma,* and *lipoma* are occasionally observed; sometimes these form polypoid growths and in other cases the neoplasm is sessile. Of the 175 cases of *sarcoma* of the alimentary canal collected by Corner and Fairbank, 58 were in the stomach. Gastric sarcoma may be subserous and pedunculated; about one-third involve the pyloric region. Pyloric constriction and obstruction are less frequent than in cancer. Approximately thirty-three per cent. of gastric sarcomata undergo metastasis to the lymph-nodes. Some of these tumors contain an unusual amount of smooth muscle-fibers, and are called by some writers malignant myomata, or myomata of the stomach.

INTESTINE.[1]

The normal intestine is lined throughout by a single layer of nonciliated, tall, cylindric epithelial cells; the submucosa is abundant and richly vascular. Situated in the mucous membrane of the intestine are many small, isolated areas of lymphoid tissue, constituting what are known as solitary glands; when these are agminated, the resulting masses are known as the Peyer's patches. The absorbing surface is enlarged by the presence of villi and folds; these structures also increase the susceptibility of the intestine to injury and disease.

Malpositions of the intestine are either congenital or acquired. The former may depend upon abnormalities in the tube, mesentery, or abdominal wall. According to Grant,[2] most of the reported congenital malpositions, exclusive of hernia, result from abnormal mesenteric attachments He reports a case in which the mesentery and colon were on the left side; the ascending and descending portions of the colon were apposed. The positions and relations of the intestine are reversed in situs inversus viscerum.[3] In some cases the cecum is abnormally mobile; the appendix may be behind the caput coli. Of the acquired malpositions of the intestine, enteroptosis, volvulus, hernia, and intussusception should be mentioned. The causes of **enteroptosis** are essentially the same as those of splanchnoptosis, given on page 431. Possibly an abnormally long mesentery favors the condition. **Volvulus** may be acute or chronic; by some, the latter is made to include twists that persist, and also recurrent volvulus.[4] In simple volvulus the gut is twisted either on its own axis or on the axis of the mesentery, and in compound volvulus two loops of the gut are entangled. Among the causes of this peculiar form of torsion are long mesentery, physiologic and pathologic elongation of the bowel, intestinal adhesions, violent peristalsis, such as accompanies indigestion, chronic intestinal obstruction, and violent exertion throwing particular stress upon the abdominal muscles. In some cases the torsion involves the entire mesentery. Of 121 cases included in Gibson's paper, in 36 the small intestine was

[1] The important literature bearing on diseases of the intestine will be found in the following works: Nothnagel's "Encyclopedia of Practical Medicine," American edition, volume on "Diseases of the Intestines and Peritoneum," 1904. Hemmeter, "Diseases of the Intestines," vol. i, 1901; vol. ii, 1902.

[2] "Amer. Med.," April 26, 1902.

[3] Reichelmann, "Deut. Zeit. f. Chir.," 1904, Bd. lxxiv, p. 345.

[4] Kirchmayr, "Wien. klin. Woch.," Oct. 23, 1902, p 1138. Moynihan, 'Med. Chronicle,' Feb., 1903. Vaughan, "Amer. Jour. Med. Sci.," May, 1903.

affected; 58 involved the sigmoid flexure, and 15 other parts of the colon. Chronic and recurring forms usually affect the sigmoid flexure. Volvulus may occur in hernia. If unrelieved, the twisting occludes the veins and, to a lesser degree, the arteries, collapses the gut at the point of pressure, and terminates in gangrene. In chronic cases neither the circulation nor the intestinal lumen are continuously obstructed, although the latter may be temporarily obliterated.

The terms **hernia** and **rupture** are applied to conditions in which a viscus or part of a viscus protrudes from the cavity in which it is normally contained. As commonly employed, the term hernia means a protrusion of the intestine or the omentum through or into some part of the abdominal wall. A hernia is composed of a sac, the contents of the sac, and its covering. Usually the *sac* is made up of the peritoneum, which is forced before the misplaced viscus. As a rule, at some point in its course the sac is narrowed; the area of narrowing is usually a constriction situated in the abdominal wall, and is called the *neck of the sac*, the *body* being that portion external to the constriction. The *covering of the sac* depends upon the location, and usually consists of the skin and the various underlying fasciæ. The sac may contain intestine (**enterocele**), omentum (**epiplocele**), or intestine and omentum (**entero-epiplocele**). Occasionally a hernia contains the bladder, stomach, large or small intestine or parts of both, appendix, ovary, etc.

Of the many causes alleged to be operative in the production of hernia, congenital weakness or defects in the abdominal wall are most important. Such defects are most common in the inguinal, femoral, and umbilical regions. An unusually long mesentery, as in enteroptosis, coloptosis, gastroptosis,—splanchnoptosis,—predisposes to hernia. Weakening of the abdominal wall as a result of cicatrices, overdistention, muscular atrophy, etc., favors the occurrence of hernia. Muscular exertion that increases the intra-abdominal tension is usually termed an exciting cause; such effort is typified in straining at stool, and lifting heavy burdens.

Hernias are said to be *reducible* and *irreducible*, depending upon the possibility of returning the displaced viscus to the abdominal cavity. Reducible hernias may become *incarcerated* as a result of accumulation of feces in the intestine, with or without the presence of gas. Phenomena of incarceration are, however, more frequent in irreducible hernia. As a result of overdistention or contraction of the ring or neck of the hernia, inflammation, or other causes the circulation becomes impeded or interrupted, giving rise to what is called *strangulated hernia*. A division of hernias into *internal* and *external* is sometimes made. The former include those in which the space containing the displaced viscus is within the trunk cavity; for example, diaphragmatic and retro-abdominal hernia. External hernias, as the name indicates, are those in which an external tumor is recognizable. The division is arbitrary, as many of the so-called external hernias may not be sufficiently marked to be recognized except by operation or postmortem. With regard to the site, hernias are said to be inguinal, femoral, umbilical, ventral, lumbar, obturator, sciatic, perineal, pudendal, and diaphragmatic. About 80 per cent. to 85 per cent. of the hernias are inguinal; 10 per cent. to 12 per cent. femoral; and about 5 per cent. umbilical; in 642 herniotomies Gibbon found 21 in which the cecum or appendix entered the sac.

Increase in the volume or displacement of the solid viscera influences the position of the intestines. The enlarged uterus of pregnancy and also pelvic tumors displace the intestine upward; greatly enlarged liver forces them to the left and downward; and when the spleen is affected, the direction of the displacement is reversed. Alglave[1] has shown that prolapse of the right kidney displaces the ascending colon and often causes adhesions which may produce obstruction. Cysts and solid growths in the mesentery and retroperitoneal tumors may alter the position of the mesentery and proportionately disturb the relations of the intestine.

Malformations of the Intestine.—Congenital narrowing, or **stenosis,** and imperforate areas, also called **atresias,**[2] occur; sometimes definite parts of the gut are absent. (See Plate XX, Fig. 1.) The most common of these malformations is situated near the anus, which, with more or less of the rectum, may be absent; or the anus may open into a sac which does not connect with the colon above. Membranous septa, transverse or longitudinal, are sometimes present. Occasionally the anus is absent and the rectum ends in a blind pouch, or opens into the bladder, urethra, or vagina. Stenosis or atresia involving the intestines is much less frequent; in the duodenum there are 48 recorded instances of atresia and 9 of stenosis. Silberman has been able to collect 30 instances of atresia of the jejunum and 3 of stenosis. In most instances the upper end of the ileum is affected; usually the atresia is single. Congenital narrowing or occlusion of the colon is exceedingly rare. Atresia and stenosis have been attributed to intrauterine intussusception, volvulus, embolism or obliterative arteritis affecting branches of the mesenteric vessels, abnormal occlusion of Meckel's diverticulum, and fetal peritonitis. Clogg believes that most instances of duodenal malformation are produced by abnormality in the buds from which the pancreas and the liver are developed. Atresias and stenoses in the lower part of the ileum are probably due to developmental errors in obliteration of Meckel's diverticulum.

Intestinal diverticula may be congenital or acquired. The most common of the former is the persistence of more or less of the omphalomesenteric duct, and is called **Meckel's diverticulum.**[3] Mitchell found it in 2 per cent. of 1635 autopsies. It may occur in any part of the alimentary canal from the esophagus to the colon, but is most common in an area beginning 15 cm. above the ileocecal valve and extending upward 150 cm. When the entire duct persists, and is patulous, an omphaloenteric fistula results. When closed at the intestinal end and open at the umbilicus, the condition is called an omphalic fistula or sinus. If closed at both ends, a cyst is usually formed; if the resulting cavity lies in front of the peritoneum, it is called a **preperitoneal cyst,** and when attached to the intestine, an **enterocystoma.** In some cases a cord, resulting from persistent vestiges of the omphalomesenteric vessels, occupies a region corresponding to that in which Meckel's

[1] "Rev. de Chir.," Dec. 10, 1904, p. 730.

[2] Kuliga, "Ziegler's Beit.," 1903, vol. xxxiii, p. 481. Krauter, "Arch. f. klin. Chir.," 1904, Bd. lxxiii, H. 4. Archambault, "Albany Med Annals," July, 1904. Clogg, "Lancet," Dec. 24, 1904, p. 1770

[3] Moore, "Jour. Amer. Med. Assoc.," Oct. 4, 1902, p. 810. Dreyfuss, "Münch. med. Woch.," Oct. 4, 1904, p. 1785. Bunts, "Annals of Surgery," Oct., 1904, p. 536.

diverticulum is usually found. The diverticulum varies in size from a teat-like projection to a cylindric body 20 cm. to 30 cm. long; the average length is about 7 cm. The point of origin is usually opposite the mesenteric border, but occasionally it is intramesenteric. Sometimes the free end is bifid, trifid, or lobulated. Often the presence of the body is unattended by symptoms; it may, however, contain foreign bodies, ulcerate and even perforate, become adherent to other parts of the intestine or abdominal wall, strangulate, or inflame (**diverticulitis**). Dobson has collected thirteen cases in which it was inverted and caused intussusception. Ekehorn states that it has been found in twenty-two hernias. Typhoid lesions situated in a diverticulum have been known to perforate, and the ulcerative and inflammatory lesions which affect it are not unlike those involving the appendix. Other diverticula of congenital origin occasionally occur in the intestine. Hedinger[1] reports a case of congenital diverticulum in the appendix. **False diverticula**[2] are hernias of the mucosa through weakened spots in the muscular wall. It is generally held that the true diverticula are congenital; the false, acquired. The walls of the former contain all the structures of the intestinal tube; the latter do not. Usually the false sacs are situated near the mesenteric attachment, into which they often project. It is probable that hernia of the mucosa occurs around or by the side of a vessel penetrating the muscle-layers. In the case reported by Condit there were two rows of pouches, each diverticulum about 1 cm. in diameter; Virchow reported a case in which the sac was the size of a hen's egg. They frequently contain fecal matter, and sometimes inflame and perforate.

Dilatation of the intestine may result from congenital or acquired conditions. The **acute paralytic distention** (**enteroplegia**) I have considered with acute dilatation of the stomach (p. 707). Congenital flap- and valve-like projections of the mucosa may obstruct the flow of the intestinal contents and produce dilatation above. **Megacolon,**[3] **congenital hypertrophy** and **dilatation** of the colon, and "Hirschsprung's disease" are names applied to an enlargement of the large intestine believed to be of congenital origin. In the case reported by Formad the colon contained 22 kilos (47 pounds) of feces. In Fütterer's patient the large intestine measured 66 cm. in circumference. In 4 of Duval's cases the condition was congenital; in 38 it began in infancy, and in 5 the symptoms appeared later. No obstruction can be demonstrated; the wall of the colon is thickened, and eventually necrotic and inflammatory processes involve the mucosa. The cause of the condition is undetermined, although its congenital origin is generally conceded. **Acquired dilatations** of the intestine develop on the proximal side of any obstruction, and, if formed slowly, may be attended by hypertrophy of the muscle-layer. In other cases there is no increase in the thickness of the bowel-wall; on the contrary, a progressive thinning occurs. As chronic obstructions usually occur in the colon, this organ

[1] "Virchow's Archiv," 1904, Bd. clxxviii, p 25. See also Hyde, "Amer Jour. of Obstet.," Dec., 1904.

[2] Fischer, "Jour. of Exper. Med.," 1901, vol. v, No. 4. Condit, "N.Y. Path Soc.," April 9, 1902. Beer, "Amer. Jour. Med. Sci.," July, 1904.

[3] Cheinisse, "La Sem. Med.," Nov. 16, 1904. "Annals of Gyn. and Pediatry," Boston, Jan. 19, 1904. Gourévitch, "Prag. med. Woch.," Nov. 24 and Dec. 1, 1904.

is most frequently dilated. Atonic forms have been described. Acute dilatation develops suddenly and is usually the result of some rapidly acting cause. It is sometimes a sequence of chronic dilatation and fecal accumulation, the latter suddenly impacting the intestine at the point of narrowing. Chronic dilatation is insidious, often persisting for months, and is commonly attended by obstinate constipation.

Intussusception[1] or **invagination** is a condition in which one portion of the intestine is invaginated within an immediately continuous part. The affection may be acute or chronic, and the intussusception single or multiple. It is probably due to irregular muscular contrac-

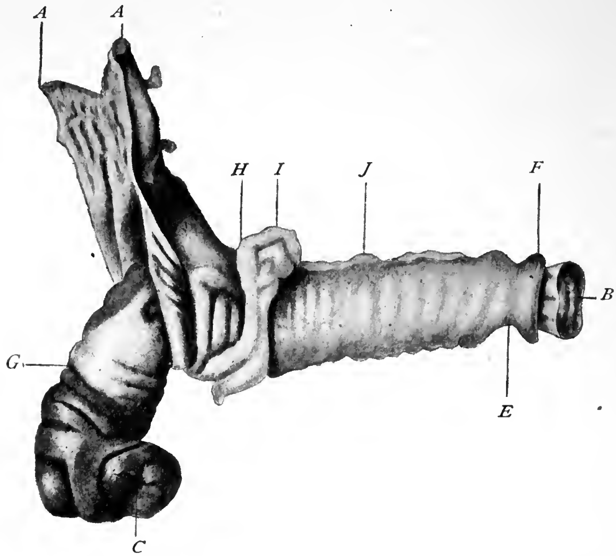


FIG 350.—INTUSSUSCEPTION AT ILEOCECAL VALVE. (Drawing of specimen from Dr. Graham's case of intussusception; operated on by Dr. Hearn.) (Compare with Fig. 351. The letters have the same significance in both figures.)

A, *A*. Colon. *B*. Point where the ileum enters the intussusception. The leader from the letter *B* points directly within the intestinal lumen. A probe passed in at *B* comes out at *C*, which is the apex. The diagram illustrates the course that it must pursue. *E*. The point of constriction of the ileum, also called the neck of the intussusception. *F*. Point of slight eversion where the serous coat turns to pass within the bowel. *G*. Shows the line of constriction in the ileum caused by the ileocecal valve. *F* to *H*, is the external layer, called the ***intussuscipiens;*** the enclosed part of the intestine, including both inner layers, from *B* to *C*, is the ***intussusceptum***. The specimen has been pulled through the valve to show this line of constriction and the gangrenous mass of intestine beyond, extending from *G* to *C*. This point of constriction in the diagram is indicated by a slight depression at *G*. *H*, *I*, and *J* show the line of attachment of the mesentery. Between *H* and *I* and extending slightly beyond the line *I*, is a fold produced by pulling the intestine through the ileocecal valve sufficiently to show the gangrenous process. (Scale, one-half the natural size.)

tion and intestinal spasm, and is not thought to be of paralytic origin, although formerly this view was generally held. Riddell[2] reported three cases occurring in a family of four children, and suggests that there may be some congenital defect that favors intestinal invagination. Active purgation, intestinal irritation, diarrhea, polypoid tumors, stenosing ulcers, and even jolts are believed to be etiologic factors.

[1] Douglas, "Surgical Diseases of the Abdomen," 1903, p. 170. Hemmeter "Diseases of the Intestine," 1902, p. 356. Corner, "Annals of Surgery," Nov. 1903, p. 690.

[2] "Brit. Med. Jour.," Jan. 10, 1903, p. 72.

Morbid Anatomy.—At autopsies one part of the intestine is frequently found invaginated within another, but there is no evidence of inflammation or vascular obstruction, and the condition is usually believed to have arisen during the agonal period, or postmortem. Several forms of the disease are recognized: **enteric invagination** occurs in the small intestine; when the ileum is invaginated through the ileocecal valve the condition is called **ileocolic intussusception**; in **ileocecal intussusception** both ileum and cecum are invaginated and the valve of Bauhin forms the apex of the intussusceptum; when the affection is restricted to the colon, it is called **colic invagination.** A section through the involved gut discloses three intestinal layers: the outer

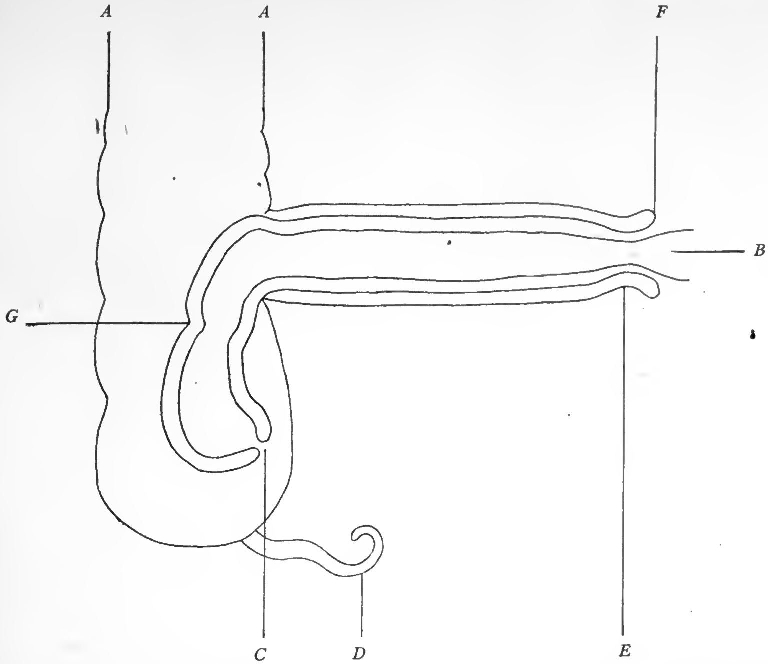


FIG. 351.—INTUSSUSCEPTION DIAGRAM INTENDED TO SHOW THE RELATION OF THE SEVERAL PARTS IN FIG. 350. The outlines of the caput coli and of the appendix have been added in order to indicate more clearly the relations. *D.* The appendix. The letters have the same significance as in Fig. 351.

is known as the *intussuscipiens*, or sheath, and the inner two constitute the *intussusceptum*. At the point where the intussusceptum enters the intusstscipiens there is usually a constriction called the *neck*. The part of the intussusceptum farthest from the neck is known as the *apex*. In double intussusception a previously invaginated portion is carried onward *en masse*—intussuscipiens and intussusceptum—into the intestine below. Sometimes the invaginated portion of the intestine is of great length; the ileum may pass through the ileocecal valve and present at the anus. As a result of constriction at the neck the circulation is impeded or arrested, and the intussusceptum undergoes necrosis, is separated, and may be discharged. Hermes records an instance in

which 60 cm. of the intestine came away as a slough and the patient recovered. In such cases an adhesion forms at the neck of the invagination and prevents escape of the intestinal contents into the abdominal cavity. The rapidity with which adhesion occurs is indicated by the fact that at operation, within twenty-four hours following the intussusception, ninety-four per cent. of the invaginations can be disinvaginated; by the second day the percentage does not exceed eighty, and by the fourth day about one-third can be restored. The swelling in the intussusceptum and the contraction of the intussuscipiens nearly always are sufficient to cause obstruction. Gibson found in 1000 cases of intestinal obstruction 121 (12 per cent.) due to intussusception, and Treves places the percentage higher. Invagination is much more frequent in children than in adults. Of Leichtenstern's 593 cases, 134 of the patients were in their first year. In about fifty per cent. of the cases the ileum is invaginated into the colon. In the 14 cases recorded by Corner 11 were double.

Intestinal obstruction[1] results from any condition which impedes or arrests the contents of the bowel. (See Plate XX.) Congenital stenosis and atresias, hernia, volvulus, and intussusception may obstruct the gut. In Gibson's study of 1000 operative cases 35 per cent. were due to hernia, 19 per cent. to constricting bands, 19 per cent. to intussusception, and 12 per cent. to volvulus. Stasis of the intestinal contents occurs in paralysis of the bowel. The condition may also be produced by foreign bodies, fecal masses, and lumbricoid worms. A single large biliary concretion, or congeries of gall-stones, may obstruct the bowel, particularly at the ileocecal valve; according to Barnard, one case of obstruction in forty-five is due to gall-stones. The intestine may be occluded by external pressure due to tumors, cysts, or wandering viscera and also by angulation. (See Fig. 238, p. 472.) Neoplasms and cysts, stenosing inflammations, cicatrized ulcers, and healing gummata may narrow the lumen of the bowel. Reed reported an instance of obstruction due to chronic intussusception produced by multiple polypi. Adynamic obstruction results from paralysis of the bowel, which may be due to changes in the muscle-layer, altered innervation, or to thrombosis or embolism of the nutrient vessels. Distal to the obstruction the bowel is approximately empty, and above the obstruction is distended. The distention in chronic obstruction may be extreme, and is usually most marked at or near the occlusion. At the point of obstruction the mucosa and intestinal wall are often anemic and frequently necrotic; above the occlusion marked congestion, erosions of the mucosa, and commonly larger areas of necrosis are observed. In the intestinal contents bacteria accumulate in large numbers and produce highly toxic substances, the absorption of which gives rise to the fever and accompanying visceral lesions. Clairmont[2] has shown that the toxic substances within the bowel are among the most active of the bacterial poisons. These poisons also nullify the inhibiting influences in the intestinal wall, bacteria rapidly migrate, and peritonitis, often without perforation, promptly

[1] Gibson, "Annals of Surgery," vol. xxxii. See also references to atresia, stenosis, volvulus, and intussusception.

[2] Quoted by Carwardine, "Practitioner," Jan., 1905, p. 87. See also Barker, "Lancet," Sept. 17, 1904, p. 807, and Albeck, "Arch. f. klin. Chir.," Bd. lxv, H. 3, p. 569.

PLATE XX.

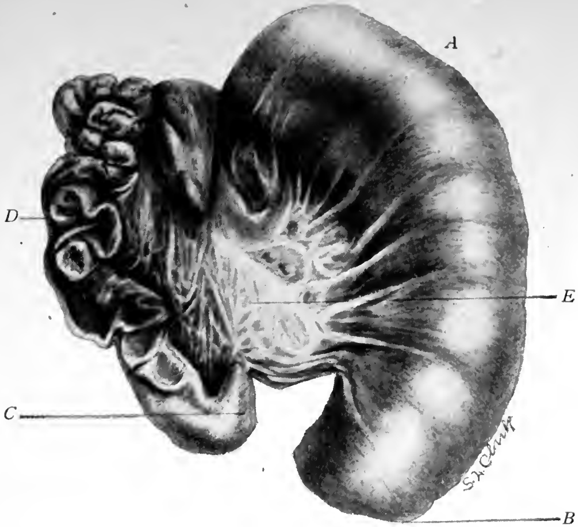


FIG. 1.
ATRESIA IN UPPER THIRD OF ILEUM. (Two-thirds natural size.)

A. Upper distended part of the ileum. *B*. Blind pouch terminating the upper segment. *C*. Closed upper end of the lower segment. *D*. Collapsed ileum below the atresia. *E*. Mesentery in which are a number of slightly enlarged lymph-nodes.

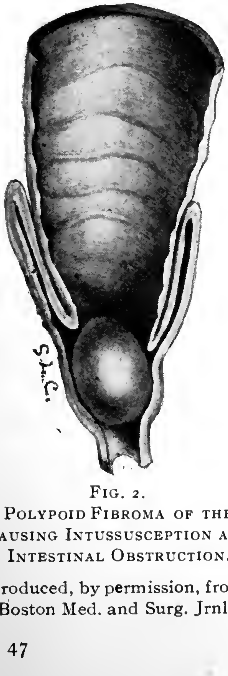


FIG. 2.
SMALL POLYPOID FIBROMA OF THE ILEUM CAUSING INTUSSUSCEPTION AND INTESTINAL OBSTRUCTION.

(Reproduced, by permission, from the Boston Med. and Surg. Jrnl.)

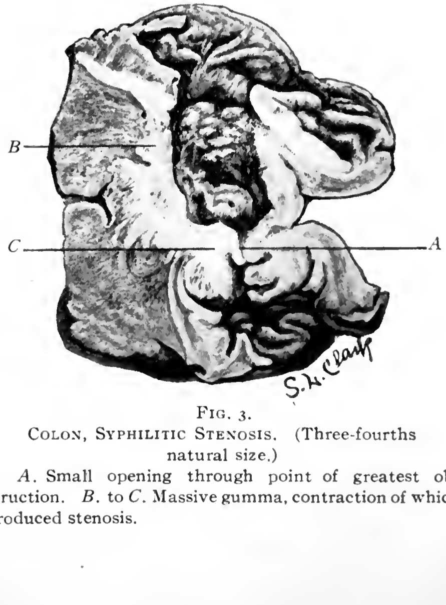


FIG. 3.
COLON, SYPHILITIC STENOSIS. (Three-fourths natural size.)

A. Small opening through point of greatest obstruction. *B*. to *C*. Massive gumma, contraction of which produced stenosis.

ensues. In chronic cases the intestine sometimes thickens; this may be due to hypertrophy and an effort to overcome the obstruction, but is often the result of cellular infiltration (Patel[1]), affecting particularly the submucosa and muscle-layers.

The **bacteria of the bowel**[2] are numerous in health and enormously increased in inflammatory conditions affecting the mucosa. Members of the colon group are always abundant; pyogenic cocci, streptococci, Bacillus pyocyaneus, and several anaerobic organisms are usually present. Friedman found the Bacillus aërogenes capsulatus in nine of sixteen examinations. Ordinarily the inhibiting influence of the mucosa is sufficient to protect the tissues from infection, but disturbances in the intestinal circulation and secretion appear to exalt the virulence of some of the contained bacteria and to lessen the resistance of the affected structures. It has been demonstrated that the colon bacillus obtained from an inflamed intestine is more virulent than when cultivated from healthy organs.

Hyperemia of the intestine occurs in acute inflammatory conditions, around areas of infarction, neoplasms, and ulcers; the blood-supply is also increased during digestion. Intestinal hyperemia also accompanies peritonitis.

Congestion of the intestine results from thrombosis of the portal vein or its branches, venal distomatosis, diseases of the liver which produce portal obstruction, and cardiac and pulmonary affections in which the venous tension rises. At autopsy dependent knuckles of the intestine often show hypostatic congestion and may be red, purplish, or almost black, from the large amount of contained blood; such areas must not be mistaken for antemortem lesions. In congestion the intestinal mucosa is intensely reddened, often purplish, and is frequently edematous. Slight epithelial desquamation is present, and necrotic changes in the lymphoid follicles are sometimes observed. In chronic congestion and in malaria the mucosa is sometimes pigmented.

Mesenteric thrombosis and embolism are usually followed by hemorrhagic infarction[3] of a segment of the intestine the vascular supply of which is affected. Endocarditis, arteriosclerosis, and other causes of embolism are usually present. Clinically the condition resembles obstruction, largely because the propulsive power of the involved area is quickly lost. According to Galivardin, septic embolism of the mesenteric arteries may give rise to aneurysm, abscess, or mesenteric hemorrhage. With the development of infarction, hemorrhage into the intestine usually occurs, the mucosa quickly undergoes necrosis, the intestinal wall softens, and is rapidly permeated by bacteria; should the patient survive sufficiently long, peritonitis develops.

Intestinal hemorrhage accompanies inflammations, ulcerations, and necroses affecting the mucosa. The bleeding may come from duodenal ulcers and from typhoid, tuberculous, and neoplastic ulcerations. Blood

[1] "Rev. de Chir.," March, 1902.

[2] Friedman, "Trans. Chicago Path. Soc.," 1902, vol. v, No. 8, p. 172. Metchnikoff, "Bull. de l'Inst. Pasteur," 1903. Ford, "Studies from the Royal Victoria Hospital," Montreal, 1903, vol. i. Lanz and Tavel, "Rev. de Chir.. " July 10, 1904, p. 43. Hewetson, "Brit. Med. Jour.," Nov. 26, 1904, p. 1457.

[3] Osswald, "Deut. Zeit. f. klin. Med.," vol. liii. Audistère, "La Progres Méd.," April 2, 1904. Jackson, Porter, and Quinby, "Jour. Amer. Med. Assoc.," June 4, 1094, p. 1469.

in varying quantities is constantly present in some stage of dysentery, and in gangrenous lesions, infarction, intussusception, and occasionally in other forms of intestinal obstruction. Intense hyperemias and chronic congestions rarely cause abundant bleeding. The quantity of blood may be large, or the hemorrhage may be of the occult[1] type. Abundant hemorrhage in the upper portion of the intestine gives rise to tarry stools. When the blood comes from the sigmoid or rectum, it may be but slightly altered by the digestive action of the intestinal juices.

Enteritis is an inflammation of the small intestine; when the large bowel is involved, the condition is called **colitis,** and when both are affected, **enterocolitis** or **ileocolitis.** Other regional divisions of intestinal inflammation are *duodenitis, jejunitis, scolecitis* or *appendicitis, typhlitis* or *cecitis* (cecum), and, when the rectum is involved, *proctitis.* Etiologically and anatomically the inflammations of different parts of the intestine are characterized by essentially similar conditions. One part is rarely inflamed for any length of time without involvement of other areas; the cause in each instance may be the same.

Acute catarrhal enteritis, also called acute intestinal catarrh, results from various forms of intestinal irritation; indiscretions in diet, intemperance, and food containing bacteria or certain types of microbic poisons (ptomains, tyrotoxicon) are capable of inducing intestinal inflammation. Climatic conditions also exert important influences in the production of inflammation of the intestine. The disease is especially frequent in children, in whom it is commonly produced by indigestible milk or milk containing bacterial products. Streptococcic infections of the udder of the cow often infect the milk, which, in turn, induces an acute catarrhal enteritis in bottle-fed children. The Bacillus dysenteriæ, Bacillus enteritidis, and highly virulent colon bacilli are usually present in the intestine; various members of the proteus group and streptococci are often found. A catarrhal enteritis of a mild grade may accompany infectious diseases, such as typhoid and pneumonia, and a severe serous catarrh results from infection by the cholera spirillum.

Morbid Anatomy.—The mucosa shows various degrees of hyperemia, which is usually more marked in adults than in infants. Usually, in protracted cases, erosions occur, and, in prolonged or intense infections, definite ulcers are sometimes formed. In other instances the lymphoid follicles are distinctly enlarged (**follicular enteritis**). When the resulting intestinal discharges are rich in serum, the condition is called **serous enteritis.** The structural alterations are those of acute catarrhal inflammation (p. 546); the mucosa is swollen, varying numbers of leukocytes are present in the submucosa, and epithelial desquamation is often conspicuous. Microscopic and even macroscopic hemorrhages are occasionally present.

Chronic catarrhal enteritis, or chronic intestinal catarrh, usually follows a succession of acute attacks, in which case the perpetuation of the inflammation is often due to chronic congestion, tuberculosis syphilis, chronic renal disease, and other affections in which nutrition and excretion usually suffer.

Morbid Anatomy.—The changes are essentially the same as those accompanying chronic catarrhal inflammations of the mucous membranes (p. 548). Follicular enlargement, erosions, and even ulcers are

[1] See Occult Hemorrhage, p. 699.

sometimes present. Submucous hyperplasia and consequent atrophic changes in the overlying mucosa are frequently found in protracted cases.

Pseudomembranous, hemorrhagic, and **gangrenous forms** of enteritis are not common. Except in the specific diseases, ulceration is rarely extensive, and simple erosion is infrequent. The causes are similar in kind to those producing catarrhal lesions, and the anatomic changes follow the general outline indicated on p. 557. Suppurative or **phlegmonous enteritis** has been described, but is exceedingly rare. In profound sepsis, especially in pyemic conditions, submucous abscesses or even more extensive infiltrations are sometimes observed. In all forms of intestinal inflammation some enlargement of the mesenteric lymph-nodes usually occurs; these structures are particularly affected in certain infectious diseases, and are especially prominent when typhoid and tuberculous ulcerations involve the bowel.

Appendicitis may be characterized by an inflammation of the mucosa or of the interstitial tissue, from which extension to the peritoneum frequently occurs. **Catarrhal appendicitis** is either acute or chronic; it may result from extension of inflammatory processes from the colon, or arise independently. No doubt faulty drainage, narrowing of the colonic orifice of the appendix, and the presence of unusually virulent organisms are important factors in its production. Foreign bodies and appendicular concretions are not without influence, although their importance has been exaggerated. Some cases are traceable to injury. The colon bacillus is present in about seventy-five per cent. of the acute cases and in eighty-five per cent. to ninety per cent. of the chronic. Pyogenic cocci, pneumococci, Bacillus pyocyaneus, typhoid bacillus, and, less frequently, the colon bacillus[1] occur without the presence of any other organism; usually a number of bacteria are found.

Catarrhal appendicitis may be acute or chronic, and no doubt in all forms of appendicular inflammation the mucosa is involved. The swelling attending acute catarrh narrows the orifice of the appendix, interferes with drainage, thereby leading to the accumulation of bacteria and their products, and in this way favors infection of the submucosa, disturbance of the circulation, and, in marked cases, gangrene. **Chronic catarrhal appendicitis** may follow the acute or develop insidiously; the mucosa wastes, the submucous connective tissue increases, and the cellular infiltration is often quite as marked as in the acute forms, although the edema is usually less. In both the acute and the chronic form of appendicular inflammation erosion and even necrosis of the mucosa frequently occur, giving rise to definite ulcers (**ulcerative appendicitis**). In other cases pyogenic bacteria infiltrate the submucosa, polymorphonuclear leukocyte accumulation occurs, local areas of necrosis develop, and in this way small abscesses are formed in the wall of the appendix; this is called **suppurative appendicitis.** The abscesses may open into the lumen of the tube, the pus drain away, and ulcers remain. In other cases the suppurative process extends toward and perforates the serosa (**perforative appendicitis**). It is also possible for ulcerations and other forms of necrosis to open the appendix, and hence perforative phenomena may be present in almost any form of severe appendicular inflammation. Bacteria retained in the cavity or

[1] See references to bacteriology of intestines, p. 719.

wall of the appendix may gradually propagate toward the surface (propagative infection) and involve the serosa, when no lesion amounting to perforation can be demonstrated. A most important type of appendicular inflammation is that attended by the formation of necrotic areas or gangrene of the appendix (**gangrenous appendicitis**). The condition is fulminatingly acute, but may be engrafted upon, or constitute a terminal stage in other forms of appendicitis. It is probably the result of intense infection, or thrombophlebitis, or autochthonous embolism affecting the vessels of the organ. The area of necrosis may be small, giving rise to a circular or funnel-shaped perforation, or the whole appendix may become gangrenous. Any of the foregoing processes may admit bacteria to the peritoneal cavity and induce a septic peritonitis which may be local or general. In some cases the bacteria are in numbers insufficient to produce suppuration, or it may be that the toxin alone diffuses through the appendicular wall, and in either case a chronic productive **periappendicitis** results. The serosa is thickened, adhesions are formed, and eventually the organ becomes imbedded in a dense mass of fibrous tissue (p. 473). It is probable that similar results may follow acute appendicitis, especially if the attacks are repeated. Infections of the appendix occasionally induce thrombosis of the veins; such thrombi, extending into the branches of the portal vein, produce emboli which, reaching the liver, cause hepatic abscess. Thrombus formation in the iliac artery or vein is rarely observed in appendicitis.

Cysts of the appendix result from occlusion of the orifice communicating with the colon. It is possible that in some cases the condition is congenital, and in others inflammatory. The cyst may be globular or cylindric; a specimen removed by Montgomery was nearly 20 cm. in length. The fluid contained within such cysts is either serous or mucous, and in some cases is inspissated.

Concretions within the appendix are usually due to inspissation of the secretions and rarely contain foreign bodies. The latter are not infrequently found, occurring in about four per cent. of the cases of appendicitis; usually they give rise to no important alteration, and even such sharp bodies as pins and fish-bones may be present without inducing marked structural alterations or inflammation.

Colitis (inflammation of the colon) may be associated with ileitis or occur independently of inflammation of the small intestine. The causes are, in many respects, similar, but the function of the large intestine renders it particularly susceptible to certain types of injury. The feces within the colon are firmer, their progress slower, and the opportunity for accumulation greater than in any other part of the alimentary canal. These observations apply especially to the cecum. As a result of the peculiarities just mentioned inflammation of the colon manifests a distinct tendency to chronicity, particularly if the cause be of a kind that readily adapts itself to prolonged existence within the mucosa or in the contents of the organ. The inflammations[1] involving the colon are catarrhal, pseudomembranous, hemorrhagic, and gangrenous; with the exception of the last named they may be acute or chronic.

Acute catarrhal colitis is frequently associated with inflammation

[1] See Inflammations of the Serous Membranes, p. 456.

of the ileum, in which case the condition is called ileocolitis, and, in children, is the anatomic basis of the clinical syndrome known as **cholera infantum.** The causes of acute colonic catarrh are essentially the same as those already given for acute catarrhal enteritis. The anatomic changes are also similar; the colonic affection, however, is prone to persist longer and give rise to more intense lesions. Desquamation of epithelium and superficial necrosis are frequently present. In the catarrhal colitis associated with changes in the follicles (**acute follicular colitis**) these structures are particularly conspicuous, and when the process is due to violent or prolonged irritation, and especially when bacteria are numerous, the follicular necrosis may give rise to small erosions or deeper ulcers. The mucosa is usually intensely edematous, red and injected, soft and velvety. Histologically, the interglandular connective tissue and the submucosa contain numerous leukocytes, and the

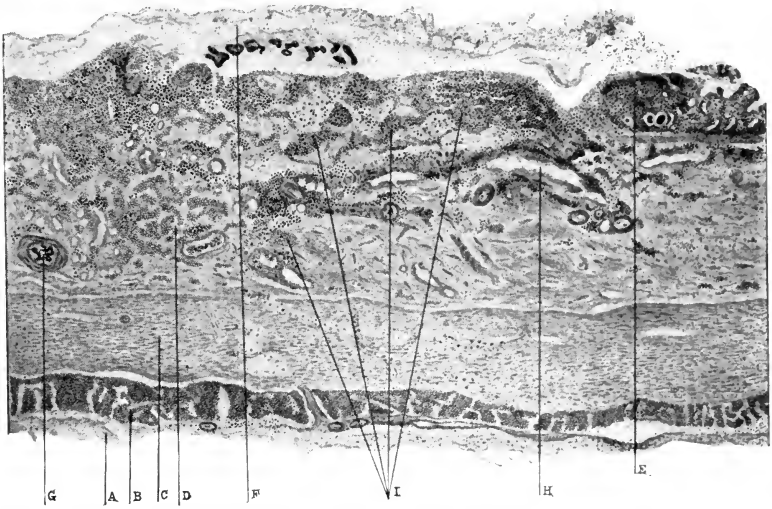


FIG. 352.—HEMORRHAGIC COLITIS.—(*Harris.*)
Death from Chronic Interstitial Nephritis. A. Serosa. B. Longitudinal muscle-layer. C Circular muscle-layer. D. Submucosa. E. Necrosing mucosa. F. Slough on the surface of the mucosa; necrotic membrane. G. Artery with exfoliating endothelium. H. Vein with softened and necrosing wall. I. Areas of hemorrhage.

epithelium of the surface and that lining the crypts is actively desquamating and often superficially necrotic. Marked hemorrhage, particularly in the dysentery cases, is often present. Sometimes the process is distributed with remarkable uniformity; in other cases it is restricted to, or is more intense in, definite areas, such as the caput coli, splenic flexure, and sigmoid. Such localization is usually determined by conditions leading to relatively prolonged contact of infectious matter with the mucosa. With the subsidence of the infection or withdrawal of other irritants the inflammation gradually subsides, the epithelium regenerates, the lymphoid structures are restored, and the mucosa may remain but slightly altered, although clinical observations indicate that its susceptibility to irritation—particularly after a number of acute attacks—is notably increased.

Chronic catarrhal colitis usually follows the acute form, and is due to persistent action of one or more of the same causes. Constitutional vices which disturb metabolism, particularly excretion, often favor perpetuation of acute lesions. It is well known that in uremia, inflammations and ulcerations of the stomach and intestine, and especially the colon, frequently occur; subjects of renal disease are not infrequently affected by chronic catarrh of the colon. Chronic catarrhal colitis is frequently a manifestation of dysentery, the causes of which I shall presently discuss. The changes occurring in this form of colon inflammation are many and varied; they are, however, of a type usually observed in chronic catarrhal inflammations of the mucous membrane (p. 548). The surface of the mucosa is often irregular, sometimes velvety, or even polypoid. In some cases marked thickening of the mucous and submucous layers gives rise to undulating irregular folds, and in other instances the formation of fibrous tissue and its subsequent contraction thin the glandular membrane and distort the tube. Ulcers are almost invariably present; in distribution they often correspond to the areas of lymphoid tissue (follicular ulceration), which usually are irregularly distributed; the margins of such ulcers are uneven and, when they extend, the contour is sometimes serpiginous; an ulcer may be enlarging in one part and healing in another. It is probable that when ulceration is marked, the antecedent inflammation was more of a gangrenous or pseudomembranous type, rather than catarrhal. The muscular layer is often thickened, the serosa may be fibrous, and the colon attached to contiguous structures. Some writers distinguish between chronic catarrhal colitis and chronic ulcerative colitis but it is probable that both are results of persistent irritation (infection, ameba) in tissue often weakened by previous local or systemic conditions. **Colitis polyposa**[1] is rare; Pope's patient had syphilis and was debilitated from other causes. Sometimes in the polypoid masses, and occasionally in the mucosa when polypi are absent, definite cysts are formed, probably from accumulation within the follicles. This condition has been called **cystic colitis.**

Pseudomembranous colitis, also called **croupous colitis** and membranous catarrh of the colon, occurs as an acute affection frequently associated with, or constituting an important part of, dysentery, and as a chronic or recurring lesion, the pathology of which is extremely obscure. The acute form is characterized by the production of a pseudomembrane lying upon and involving the superficial part of the mucosa, and composed of cellular detritus, leukocytes, and mucus, and frequently containing fibrin; the quantity of fibrin varies in different cases, and in some instances none can be demonstrated in the membrane. Flakes of membrane and sometimes sheets and occasionally casts of the colon may be passed with the feces. At autopsy areas of attached membrane are frequently present, and irregular masses are usually loose in the bowel cavity. One part of the bowel may show the lesions of catarrhal inflammation; pseudomembrane may be present in another area; and a third portion exhibits the changes usually observed in gangrenous inflammations. The infiltration of the submucosa, and cellular accumulation between the crypts, are similar to those described in the acute catarrhal inflammation.

[1] Pope, "Brit. Med. Jour.," July 23, 1904, p. 180.

The chronic recurring or relapsing colitis, also called **mucous colitis,** is an affection about the etiology and pathology of which we possess little accurate information. Particles of membrane, or even large casts, escape in the stools; the membrane is hyaline, usually structureless, and often contains no demonstrable fibrin. The disease is observed in adults, especially females, and is commonly associated with hysteria, nervous affections, and constipation. It is probable that in this group of cases a number of conditions are included, some of which are not inflammatory. Ewald believes that, in some instances at least, the condition is a neurosis, and proposes the name **myxoneurosis intestinalis membranacea.**[1]

Gangrenous colitis, also called **diphtheric colitis** and **necrosing colitis,** is often associated with pseudomembranous inflammation, and probably represents nothing more than a deeper necrosis, due to an infection of greater intensity. Large areas of the mucous membrane or irregular, smaller portions undergo a form of coagulation necrosis which may extend into the submucosa or muscular layer and occasionally involves all coats of the bowel. The necrotic tissue, after separation, leaves irregular denuded areas which, if the patient survive, are converted into ulcers. The necrotic fragments may be recognized in the stools. Opened vessels sometimes bleed profusely; septic phenomena are often marked, and the absorbed toxic products may give rise to necrotic areas in the liver and spleen, and sometimes induce an acute nephritis. Should the patient survive, chronic ulcerative processes and persistent catarrhal inflammation continue the structural alterations sometimes for months or even years. The anatomic changes leave the mucous membrane so profoundly altered that its susceptibility to all forms of irritation is greatly increased, and consequently complete recovery is uncommon.

The term **dysentery**[2] is applied to a number of affections in all of which, although the ileum may also be involved, the constant anatomic changes are situated in the large bowel. At the present time classification of the dysenteries is in a somewhat chaotic condition; this is largely the result of existing confusion with regard to the etiology, and partly on account of the difficulty in coördinating clinical, epidemiologic, etiologic, and anatomic forms in such a way as to establish definite order. Clinically, acute and chronic forms are recognized; the epidemiologist is able to detect sporadic, endemic, and epidemic forms of the affection, and those who study the etiology distinguish—(1) a type due to irritation by indigestible food, preformed poisons, and irritants of various kinds; (2) another type,—often occurring in epidemics,—clearly of an infectious nature; and (3) a series of cases in which the affection is due to the ameba. The dysenteries due to spirilla, and those induced by the Balantidium coli,[3] are so infrequent that they may be disregarded. Of the irritative or chemic dysentery, resulting from the ingestion of preformed poisons, we possess but little accurate information, and no observations justify giving it a position distinct from other forms of colitis.

[1] "Amer. Med.," Feb 13, 1904, p. 260.
[2] Broida, "Arch. de Méd. Exper.," Nov., 1903, p 820.
[3] Ehrnrooth, "Zeit. f. klin. Med.," Bd. xlix, p. 321. Klimento. "Ziegier's Beit.," 1903, Bd. xxxiii, p. 280.

Acute infectious dysentery is evidently due to some communicable factor, and, at the present time, is usually attributed to the Bacillus dysenteriæ.[1] Anatomically the alterations observed in acute cases correspond to the different types of acute colitis already described; the changes in the ileum are rarely marked. In the milder cases the lesion is catarrhal, with superficial necrosis and some follicular swelling; the hyperemia is frequently intense, and the rugæ are unduly prominent; at points ecchymosis or distinct hemorrhage may be present. Later, or in more marked cases, pseudomembrane forms, or extensive tissue destruction manifests the necrotic tendency of the process. The colon may be grayish, or greenish, and contain dusky brown areas of necrotic tissue. In cases that have persisted longer the softening and thickening of the colon are often intense, purulent collections may be found in the submucosa, and peritonitis is not infrequently present. It will be observed that the lesions do not always differentiate the affection from other types of colitis.

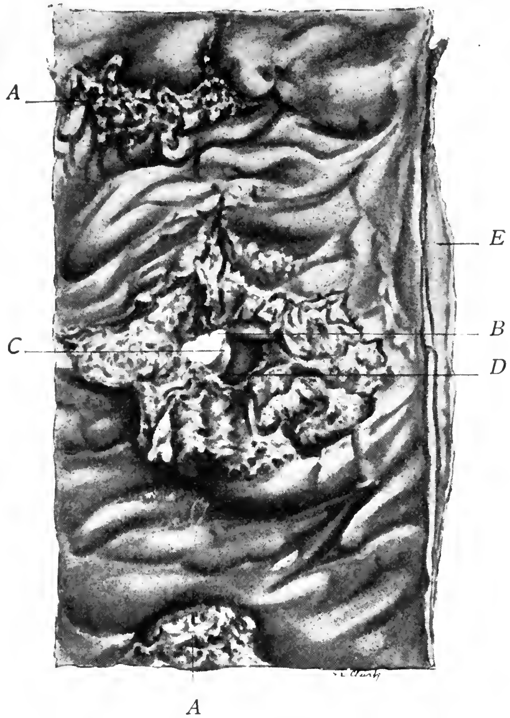


FIG. 353.—PERFORATING ULCER OF COLON (AMEBIC DYSENTERY). —(*Specimen presented to the Museum of the Jefferson Medical College by Capt. C. F. Kieffer, U. S. A.*)

A, A. Small irregular superficial ulcers extending to the submucosa only. B. Perforation of a terraced ulcer. C. Serosa. D. Muscularis. The remainder of the large irregular ulcer extends no deeper than the submucosa.

Amebic dysentery[2] involves the colon, particularly the caput coli, and occasionally the appendix. In typical cases of the disease ulceration is especially marked in the lower and anterior parts of the colon; the ulcers are irregular in outline, and the long axis often transverse to the axis of the gut. Sometimes the floors of the ulcers are honeycombed; the edges are usually undermined. The changes apparently begin in the submucosa, or at least—even before ulceration—are most marked in that structure, which becomes intensely

[1] See description of the organism, p. 141. at which point the literature bearing on the bacteriology and epidemiology of infectious dysentery is given. Also Craig, "Med. Record," May 10, 1902; "Amer. Med.," Oct. 11, 1902, p. 571, "Jour. of the Assoc. of Military Surg.," June, 1904; and "Amer. Jour. Med. Sci.," July, 1904, p. 145. Howland, "Med. News," March 5, 1904.

[2] See description of amebæ, also literature in foot-note, p. 181. Also Rogers, "Brit. Med. Jour.," June 6, 1903, p. 1315. Harris, and also Futcher, "Jour. Amer. Med. Assoc.," Aug. 22, 1902.

swollen and promptly infiltrated by mononuclear cells. The cellular infiltrate, in addition to small mononuclear cells, contains larger elements, possessing single nuclei and vesiculated protoplasm; such cells resemble ameba. Necrosis of the overlying mucosa, and often the adjacent muscularis, follows the changes in the submucosa. The amebæ are most conspicuous in the active lesion, and are rarely found in advance of the cellular infiltration. The walls of the contained vessels, especially the veins, are infiltrated by the accumulated cells, and frequently contain thrombi and sometimes amebæ. As the process approaches the serosa a fibrinous inflammation surmounts the lesion, and adhesion to contiguous

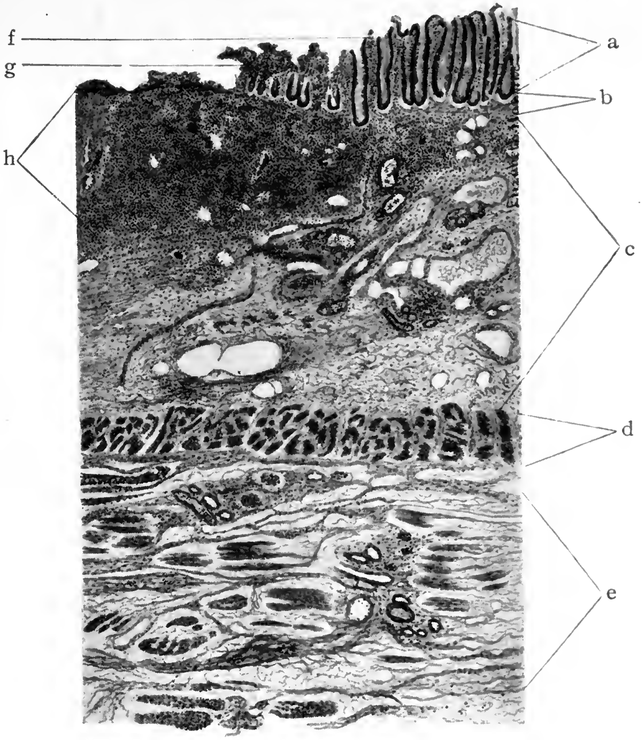


FIG. 354.—AMEBIC DYSENTERY IN PUPPY (THIRD TO FOURTH DAY).—(*Harris.*)
a–e. Coats of intestine. f. Necrosis of epithelium at margin of ulcer. g. Edge of ulcer. h. Infiltrated submucosa.

structures commonly occurs. Superficial erosion or even ulceration in which amebæ can not be demonstrated sometimes accompanies the lesion and is probably due to concurrent bacterial infection. Perforation of the intestine is infrequent. Of 2377 cases of tropic dysentery, probably amebic, hepatic abscess occurred in 19.3 per cent.

Cholera asiatica[1] is an infectious disease characterized by an inflammation of the intestine and evidences of systemic intoxication. The lesion in the intestine (p. 144) is that of an acute serous catarrh.

[1] For description of the organism and bibliography see page 142

Typhoid or **enteric fever** is not properly a disease of the intestines, although its principal manifestations commonly occur in these structures. The organism associated with the disease is described on page 238. By the administration of pure cultures of the typhoid bacillus Grünbaum[1] has produced typhoid in the chimpanzee. Dufloco and Voisin[2] report an illness, believed to have been typhoid, due to taking typhoid culture with suicidal intent.

Morbid Anatomy.—More or less marked catarrhal inflammation of the ileum and colon accompanies the other intestinal lesions; if diarrhea be present, the acute intestinal catarrh is usually more marked than when this symptom is absent. Early in the disease the lymphoid follicles become swollen and prominent; hyperemia is usually present, but often is not marked. Mallory has shown that the endothelium of the lymph-vessels and capillaries proliferates, and that fibrin is present in the affected structures. In the agminated follicles—the patches of Peyer—the hyperemic swelling and the cell proliferation are more marked and the bacillary infiltration is deeper. The patches are elevated, edematous, and surrounded by a slight zone of redness; at first the agminated node is intensely engorged and deeply colored, but later the tension within the patch rises, the vessels are occluded by hyaline thrombi, less blood enters, circulation is arrested, necrosis occurs, the slough separates, and an ulcer results. The depth of the ulcer is dependent upon the extent of the necrosis: it may involve only a part of the mucosa, but more commonly the entire thickness of the epithelial layer is destroyed, and the submucosa or muscularis is exposed. The edge of the ulcer is irregular, swollen, and, it may be, undermined; the base, after the slough has completely disappeared, is clean and

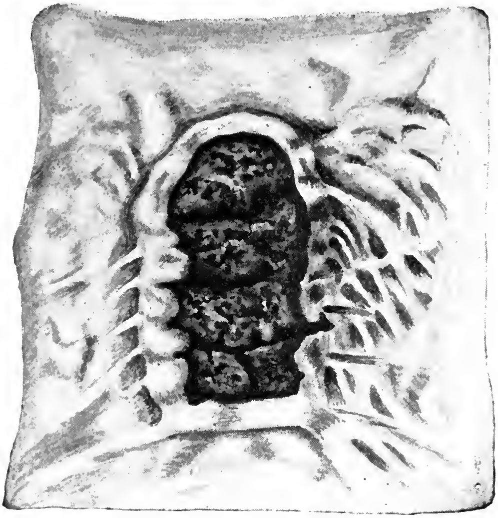


FIG. 355.—SMALL INTESTINE. TYPHOID ULCER DURING THE EARLY PART OF THIRD WEEK OF THE DISEASE. (Natural size.)

The long axis of the ulcer corresponds to that of the bowel; the base of the ulcer still contains the slough, or necrotic tissue, which is nearly ready to be thrown off; its ragged and fissured surface is well shown.

[1] "Brit. Med. Jour.," April 9, 1904.

[2] "Arch. Gen. de Méd.," Sept. 1, 1903. See also Atlassoff, "Annales de l'Inst. Pasteur," Nov. 25, 1904, p. 701. For literature on morbid anatomy of typhoid see Mallory, "Jour. of Exper. Med.," vol. iii, p. 611. Longcope, "Bull. of the Ayer Clinical Laboratory of the Penna. Hospital," Jan., 1903, No. 2. Baer, "Amer. Jour. Med. Sci.," May, 1904, p. 787. For complications of typhoid see Keen, "Surgical Complications and Sequels of Typhoid Fever," 1898 Also Hare, "The Medical Complications, Accidents, and Sequelæ of Typhoid or Enteric Fever," 190

smooth. If the sloughing process be attended by infiltration and vascular stasis in the muscularis, the necrosis may extend through the intestinal wall, or, though rarely, perforation results from extending lesions after the slough has separated. If the lesion extends through the wall of the intestine, peritonitis necessarily ensues. Yates found peritoneal inflammation, without perforation, 73 times in 4300 cases of typhoid. Perforating ulcers occur in about four per cent. to six per cent. of all cases of typhoid. If a vessel of any size be opened during the process of sloughing, or if a coagulum fails to form in a necrotic vessel, hemorrhage results. With separation of the slough, in favorable cases, repair begins; embryonic, followed by granulation tissue develops, and epithelial reproduction proceeds from the margins toward the center.

The typhoid ulcer is oval in outline, with its long diameter in the axis of the bowel; it rarely involves the entire patch, but may do so the ulcers are most abundant and most constant near the ileocecal valve but may develop in any part of the alimentary canal where the lymphoid elements are present. Chronologically, infiltration and cell-pro-

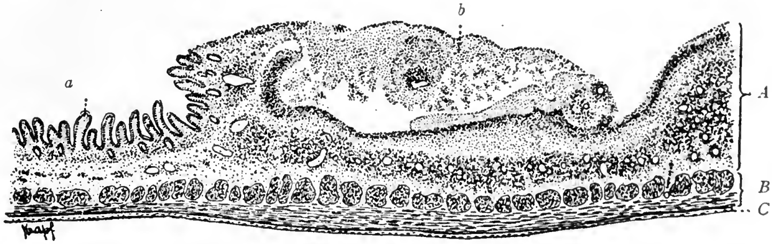


FIG. 356.—SECTION THROUGH A TYPHOID ULCER, END OF SECOND WEEK OF THE DISEASE.—(*Schmaus.*) (Partly diagrammatic.)
A. Mucosa and submucosa, the latter infiltrated with lymphoid cells. *B*. Muscle-coats of intestine. *C*. Serous layer of intestine. *a*. Adjacent nearly normal mucosa. *b*. Separating slough.

liferation terminate in necrosis about the end of the second week or in the beginning of the third week; during the latter the sloughs separate; healing may not be completed until clinical recovery has long been passed. The typhoid ulcer may occur elsewhere than in the alimentary canal; Baer found it present in the larynx in about twenty per cent. of the fatal cases. They sometimes occur in the appendix or in Meckel's diverticulum. The ulcer involves the ileum in 97.5 per cent. of the cases. Rarely no ulceration is found; Baer has collected twenty-eight cases, verified by bacteriologic examination, in which intestinal ulceration was absent.

With infiltration of the Peyer's patch, and the generation of poisons therein, the lymphatics and blood-vessels begin the absorption of toxins, whose influence may be wide-spread; at the same time the bacilli gain access to the viscera, and may be found not only in the patches, but in the mesenteric lymph-nodes, spleen, and liver, and frequently (ninety per cent. of the cases) in the blood. The mesenteric nodes are infiltrated, and occasionally necrotic; suppuration due to the pyogenic activity of the bacillus, or to mixed infection by pyogenic cocci

may occur. There are three recorded instances of ruptured[1] mesenteric node. The adjacent lymph-nodes (retroperitoneal) may be involved.

The spleen is enlarged, soft, and may show infarction, rupture, or gangrene. (See Acute Splenic Tumor, p. 434.) The liver is the seat of cloudy swelling, and quite constantly contains areas of coagulation necrosis. The kidneys exhibit a similar change, or, as a result of the intense toxemia and bacteremia, an acute nephritis may be present. The muscles of the abdomen and the adductors of the thighs are commonly altered

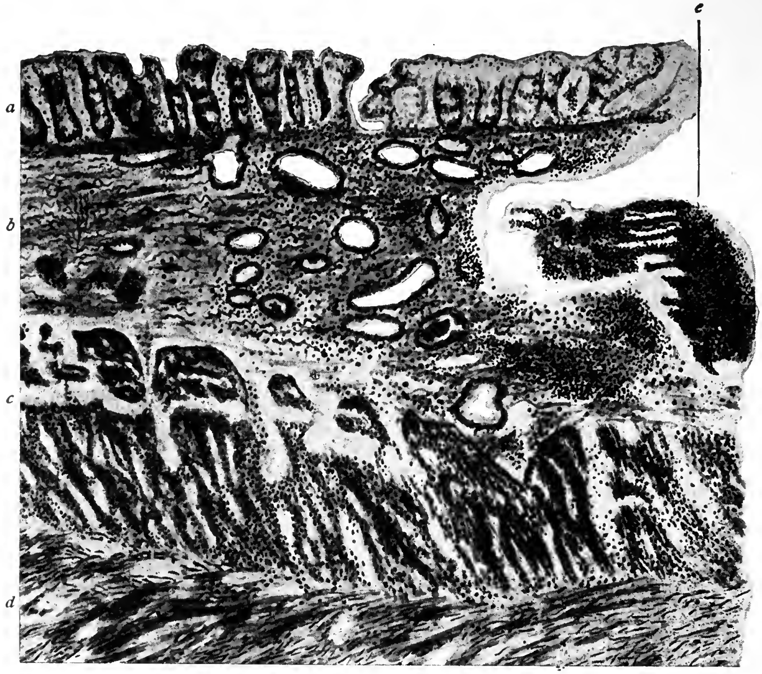


FIG. 357.—SECTION OF THE INTESTINAL WALL AT THE EDGE OF A TYPHOID ULCER, BEGINNING OF THIRD WEEK OF THE DISEASE. (Much higher magnification than Fig. 356.) (¼-inch objective; ½-inch projection ocular.) Specimen hardened in corrosive sublimate, infiltrated with paraffin, stained in hematoxylin and eosin, and mounted in balsam. *a*. Mucosa, which overhangs the margin of the ulcer. *b*. Submucosa, infiltrated with serum and containing some fibrin. Near the ulcer well-marked and extensive round-cell infiltration is seen. *c*. Transverse muscle-fibers; immediately under the ulcer these will be seen containing many round cells and are the seat of degenerative changes not discernible with this magnification. *d*. Longitudinal muscle-fibers. *e*. Slough of necrotic tissue matted together, and about separated, preliminary to being thrown off.

by hyaline or vitreous degeneration; rarely, other muscles are similarly affected. Granular change or cloudy swelling may be present in the cardiac muscle; an acute nonsuppurative interstitial myocarditis (p. 494) is occasionally observed. Changes in the bone-marrow, resembling those occurring in the lymphoid follicles of the intestine and spleen, were present in each of the twenty-six cases studied by Longcope. There was a similar accumulation of lymphoid cells and large endothelial phagocytes; foci of necrosis were also frequently present in the

[1] Le Conte, "Jour. Amer. Med. Assoc.," Oct. 22, 1904, p. 1188.

affected marrow. It is well known that suppurative processes and necroses not uncommonly occur in the bones after typhoid, and that the bacillus may be obtained from such lesions long after recovery from the initial infection. When the complication occurs during or immediately after typhoid, it might be accounted for by embolism, endothelial changes in the vessels, or thrombosis; such an explanation fails to make clear the long latent period often present; it may be that the bacteria require some accessory factor—such as injury—in order to extend the inflammatory process. The bacillus is frequently present in the biliary passages, and in some cases persists years after the attack of typhoid. It may give rise to cholecystitis, which in some instances is suppurative; gall-stones often follow typhoid infection of the gall-bladder. In addition to the cardiac changes already mentioned, endarteritis, endophlebitis, and thrombus formation are occasionally due to infection by the typhoid bacillus; endocarditis is less frequent. Thayer's[1] studies indicate that not only may typhoid produce acute lesions in the vascular system, but that it is possible for it to develop conditions which terminate in arteriosclerosis. A thrombophlebitis sometimes involves the portal vein or its branches and, though infrequently, other veins. Noma and other gangrenous processes occasionally occur.

Paratyphoid fever is an infection generally thought to be different from typhoid, but due to a closely allied organism—the **paratyphoid bacillus**[2]—of which Buxton and, more recently, Fox recognize two forms. The disease appears to be a bacteremia without constant anatomic lesions. The intestinal lesions are variable; the ulcers are described as resembling the necroses of dysentery more than those of typhoid. Splenic enlargement is present, but neither the clinical nor the anatomic picture is sufficient to distinguish the disease from typhoid; the bacilli isolated are intermediate between the colon bacillus and the Bacillus typhosus, and the diagnosis, clinical and anatomic, must be based on agglutination tests.

Syphilis of the intestine[3] occurs in both hereditary and acquired forms of the infection. Acute and chronic catarrhal conditions, attributed to syphilis, possess neither anatomic nor clinical peculiarities distinguishing them from similar manifestations arising from other causes. Syphilitic ulcerations may involve the small and large intestine, but are most frequent in the rectum. Perforation occurs, but is uncommon. The ulcers frequently result from necrotic processes affecting gummata, and, when cicatrized, usually give rise to strictures. Gumma without ulceration may also cause stenosis. Syphilitic strictures (Plate XX, Fig. 3) are usually in the rectum, and, according to Allingham and also Matthews, about half of the stenoses occurring in the rectum are of syphilitic origin. Two-thirds of the patients are women, and the condition is more common in the colored than in the white race.

[1] "Johns Hopkins Hospital Bull.," Oct., 1904.

[2] Wells and Scott, "Jour. of Infect. Diseases," Jan. 2, 1904, p. 72. Henry, "Amer. Med.," April 15, 1905, p. 613. Fox, "Univ. of Penna. Med. Bull.," April, 1905.

[3] Weiss, "Centralbl. f. d. Grenzegebiet. d. Med.," Jena, 1902, vol. v, Nos. 15 and 16. Suarez de Mendoza, "Gaz. des Hôp. Civils et Militaires," March 17, 1904. Elder, "Brit. Med. Jour.," May 7, 1904, p. 1068. Frankenburger, "Med. News," Feb. 4, 1905, p. 204.

Actinomycosis of the intestine[1] is of necessity considered with **abdominal actinomycosis** because, in many cases, it is impossible to decide whether the lesion began in the intestine or some other abdominal viscus. According to Burnam, there are 32 cases of actinomycosis of the appendix on record; the condition is called **perityphlitis actinomycotica.** Approximately sixty per cent. of the intestinal infections are in the neighborhood of the appendix. The lesion may be suppurative or neoplastic; the former gives rise to abscesses in which the fungus can readily be detected. In the second variety, tumors, which are sometimes pedunculated, are formed; neither necrosis nor abscess formation is conspicuous. The pelvic manifestations of actinomycosis often appear to arise in the organs of reproduction situated in that area, but may also result from rectal infection.

FIG. 358.—SMALL INTESTINE; SECONDARY TUBERCULOSIS; MULTIPLE TUBERCULOUS ULCERS.

Tuberculosis of the intestine[2] may be primary or secondary; the former is exceedingly rare; the latter is common in all forms of tuberculosis in which material containing bacilli is swallowed. The incidence of primary tuberculosis of the intestine is not the same for all countries, and the affection is much more frequent in children than in adults. Hunter's experience in China, where tuberculosis is common, gives the lowest percentage; he found five cases in 5142 autopsies. Wagener, in Germany, observed it in 16.4 per cent. of children under fifteen years of age; of 203 cadavers of children, examined by Orth, in only two was there reason to believe that the intestinal lesion was primary. It may affect the intestine, giving rise to characteristic tuberculous ulcers, or the bacillus passes through the intact mucosa and is deposited in the contiguous mesenteric lymph-nodes. Secondary tuberculosis of the intestine may be miliary, ulcerative, or hyperplastic.

Miliary tuberculosis of the intestine is usually a part of a general miliary tuberculosis. Sometimes the tubercles can be recognized in the submucosa, or, when the peritoneum is involved, on the serous surface. **Chronic caseous** or **ulcerative tuberculosis of the bowel** begins as an infiltration of, but is not restricted to, the adenoid tissue—usually a Peyer's patch. After

[1] Zondeck, "Deut. Zeit. f. Chir.," June, 1903, Bd. 69, H. 1. Letulle, "Revue de Gyn.," Paris, 1903, vol. 7, No. 4. Burnam, "Bull. of Johns Hopkins Hosp.," April, 1904. Bell and Harris, "Lancet," June 11, 1904, p. 1656. See also p. 166.

[2] Harris, "Annals of Surgery," Nov., 1902. Epstein, "Wien. klin. Rundschau," Feb. 28, 1904. Cullen, "Amer. Jour. Med. Sci.," March, 1904 Hunter, "Brit. Med. Jour.," May 14, 1904, p. 1126. Berard and Leriche, "Revue de Chir.," Aug. 10, 1904, p. 165. Fröhlich, "Wien. klin. Woch.," Dec. 15, 1904, p. 1344. Wagener, "Berl. klin. Woch.," vol. xlii, No. 5.

infiltration and the formation of miliary tubercles, caseation, followed by necrosis of the overlying epithelium, gives rise to an ulcer. (See p. 152.) The long axis of a tuberculous ulcer is usually, although not invariably, transverse to the axis of the intestine; this peculiarity is due to the distribution of the lymphatics and vessels along the course of which the ulceration extends. Commonly the infection is propagated through the intestinal wall, and miliary tubercles appear immediately beneath the subserosa. The edge of the ulcer is usually irregular, the margins undermined, and the floor necrotic and often containing macroscopic tubercles in which, by direct or by transmitted light, caseous centers can usually be recognized (p. 149). A catarrhal inflammation of the contiguous mucosa is commonly present. As a result of fibroid changes in the floor of the ulcer, and especially in the serosa, contraction frequently occurs, giving rise to stenosis. Perforation is infrequent. The mesenteric nodes are commonly involved and, in some cases, the retroperitoneal lymphatic tissues are also affected. Extension to the peritoneum may give rise to tuberculous peritonitis. (See p. 475.)

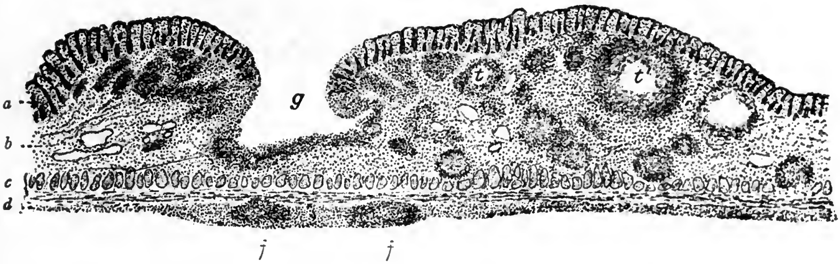


FIG. 359.—TUBERCULOUS ULCER.—(*Schmaus.*) × 12 diameters.
a. Mucosa. *b.* Submucosa, in which are numerous tubercles, *t* and *t'*; in the latter, caseation is advanced. *c.* Muscularis. *d.* Serous covering, in which, at *f*, *f*, are two tubercles. *g.* Opening of ulcer into the lumen of the canal.

Chronic hyperplastic tuberculosis of the intestine usually occurs in the neighborhood of, or is primary in, the cecum. The intestinal wall of the affected area may be enormously thickened, sometimes measuring 1 cm. from serosa to mucosa. The thickening is often the result of fibrous tissue hyperplasia in which characteristic tubercles are scanty and occasionally absent (p. 153). The overlying serosa is greatly thickened, and often is firmly attached to contiguous structures. The thickened nodule is sometimes sausage-shaped and occasionally can be felt through the abdominal wall. By parietal adhesion and extension the lesion is propagated through the belly-wall and at points opens externally, giving rise to fistulous tracks which communicate with the primary focus of the infection. Although the lumen may be narrowed sufficiently to cause obstruction, ulceration of the mucosa is not invariably present. Usually the histologic picture of tuberculosis can be identified, but sometimes characteristic tubercles and bacilli are difficult to demonstrate. The nearest lymph-nodes are almost invariably affected, although rarely is the involvement as extensive as in the caseous and

ulcerative form of intestinal tuberculosis. The condition is frequently mistaken for a malignant growth, and is amenable to operative treatment, after which an occasional patient recovers. The extensive fibrous changes are evidences of considerable resistance on the part of the patient, or infection by bacilli possessing slight virulence.

Tumors of the Intestine.—*Papilloma* is occasionally seen around the anal border, but is not common. *Adenoma*[1] may occur in any part of the canal, and is especially frequent in the rectum. It is usually solitary; occasionally two or three are present, and in rare cases large tracts of the mucous membrane are covered with these tumors. In the beginning adenoma is sessile, the surface rapidly becomes tuberous and papillomatous (papillary adenoma), and in many cases a pedicle forms. It is probable that the growth is induced by local irritation; it is not infrequently observed in venal distomatosis, in which condition the ova of the parasite are usually found in the tumors. In infancy

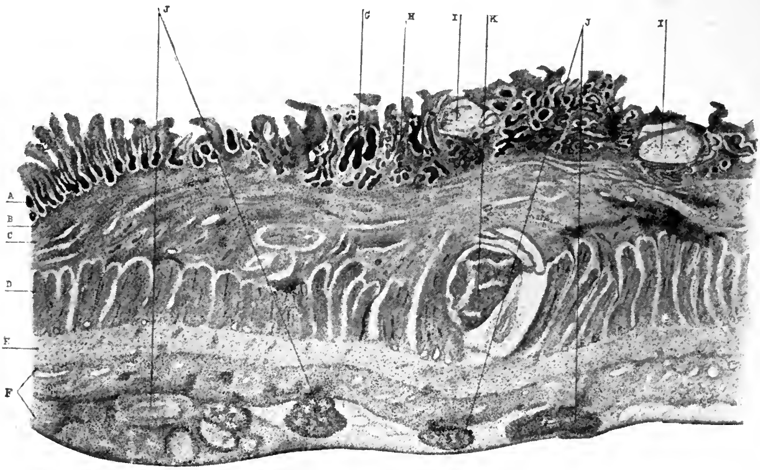


FIG. 360.—HYPERPLASTIC TUBERCULOSIS OF SMALL INTESTINE. Note the fibrous hyperplasia in the submucosa A–F. Layers of the intestinal wall. G. Irregular tubules enlarged and proliferating. H. Small crypts, branched I. Cystic dilatation of crypts. J, J. Tubercles in subserosa. K. Tubercles in circular muscular coat.

and childhood adenomata are benign, but in middle life they are frequently converted into carcinoma (p. 319). **Carcinoma of the intestine** is the most frequent tumor of the bowel; it may be situated anywhere between the duodenum and anal border, but is commonest in the rectum. Leichtenstern, in 4567 cancers, found 143 arising in the rectum and 35 in other parts of the intestine. Brill,[2] in 770 cases of intestinal carcinoma, found 33 in the small intestine. Petersen and Colmers,[3] in a study of carcinomata of the digestive tract, found 66 in the stomach, 22 in the colon, and 212 in the rectum. According to these observers cancer remains localized longer when the rectum is involved than when the stomach is affected. Of 41 duodenal cancers collected

[1] Ball, Erasmus Wilson Lectures, "Brit. Med. Jour.," Feb 21, 1903, p. 413.
[2] "Amer. Jour. Med. Sci.," Nov., 1904, p. 824.
[3] "Beit. z. klin. Chir," 1904, Bd. xliii.

by Rolleston the average age of the patients was fifty-two years. When situated in the first part of the duodenum, it is called *juxtapyloric duodenal carcinoma*; *supra-ampullary cancer* arises just above the opening of the bile-duct; *peri-ampullary carcinoma* surrounds the orifice of the bile-duct; *infra-ampullary* or *juxtajejunal cancer* occurs in the lower part of the duodenum. Of the 25 carcinomata of the colon collected by Clogg, 8 were in the cecal region, 3 in the hepatic, 6 in the splenic, and 8 in the rectosigmoid areas. There are at least 123 recorded cases of primary carcinoma of the appendix.[1] Two distinct types of cancer of the large bowel may be recognized: one in which the tumor involves several centimeters of the bowel and is soft, with little tendency to obstruct. The second form involves a smaller area, is often circumferential and usually contracts, giving rise to a stricture. Of all the cancers of the bowel, the last-named group remains localized longest. The softer tumors are usually cylindric-cell carcinomata; the denser masses are commonly scirrhous cancers. In the absence of obstruction cancer of the bowel may be latent and give rise to no symptoms prior to those due to metastasis. The great vascularity of the intestine favors infiltration of the veins, involvement of the portal branches, and, consequently, secondary growths in the liver are frequent.

Connective-tissue tumors of the intestine are uncommon. Gross[2] has been able to collect 22 instances of intestinal lipoma. Ward has increased the number to 37, but included those from all areas of the alimentary canal. They frequently become polypoid, and are sometimes detached and passed with the feces; Ray reported a case of intussusception due to a polypoid lipoma. (Plate XX, Fig. 2.) Fibromata, osteomata, and myomata are infrequent tumors of the intestine; in location they may be submucous, polypoid, or subserous. **Sarcoma** of the intestine is rare; of 106 malignant tumors involving the bowel, Mikulicz[3] found 3 sarcomata of the small intestine and 2 of the colon; the series also includes 5 carcinomata of the small and 95 of the large bowel. Of the 175 sarcomata of the alimentary canal collected by Corner and Fairbank,[4] 65 were in the small intestine, 20 in the ileocecal region, 11 in the large intestine, and 7 in the rectum. The growth may be annular, plaque-like, or polypoid, or two of these conditions may be combined. In one-third of the cases lymphatic metastasis occurred, and in 9 instances there were secondary growths in other organs. The round-cell sarcoma is the most frequent, although all types have been observed; Treves reported a case of melanotic sarcoma of the intestine. Of the 45 intestinal sarcomata collected by Lecene,[5] only 2 narrowed the lumen of the intestine.

I have already (p. 480) referred to **retroperitoneal neoplasms** and **cysts.**

The intestinal lesions accompanying **venal distomatosis** are described on page 194.

Enterolithiasis consists in the formation of definite enteroliths, or

[1] McWilliams, "Amer. Jrnl. Med. Sci.," June 1908.
[2] "Wien. klin. Woch.," Nov. 15, 1900. See also Ward, "Albany Med. Annals," Jan., 1904.
[3] "Arch. f. klin. Chir.," 1903, Bd. ixix, No. 1
[4] "Practitioner," June, 1904, p. 810.
[5] Thèse de Paris, 1904, Steinheil.

the presence, in the intestine, of finely granular earthy matter called intestinal sand. **Enteroliths** arise in sacs or pockets, such as diverticula, and in the appendix; they are composed of an organic basis, consisting of inspissated fecal matter and desquamating cells, into which calcareous salts are infiltrated. It is possible that some of the enteroliths are derived from the biliary passages or the pancreas, although it is manifestly improper to consider gall-stones and pancreatic calculi with the intestinal concretions. Analysis of **intestinal sand,** in the case reported by Bedford,[1] showed that it contained 5 per cent. of moisture, 28 per cent. of calcium phosphate, 5 per cent. of calcium carbonate, less than 1 per cent. of magnesium phosphate, and 60 per cent. of organic matter; I have omitted the fractions. McNamara suggests that intestinal sand may be due to a reversionary action of the epithelium of the rectum or colon to the egg-shell forming function of birds.

Hemorrhoids, or **piles,** are vascular masses occurring in the lower rectum and around the anal border; they are usually produced by varicose dilatation of the hemorrhoidal veins. Reinbach's contention that new vessels are formed is probably correct. The older view that hemorrhoids were due to cirrhosis of the liver and heart disease is no longer insisted upon. Von Recklinghausen called attention to the fact that, under practically all normal conditions, no matter what posture the body is in, the tension in the hemorrhoidal veins is elevated, and must be influenced by gravity; the absence of valves intensifies such action. When outside the sphincter, they are called *external piles*, and when within, *internal piles;* cutaneous piles are external hemorrhoids just beneath the skin. Injury and infection frequently give rise to a thrombophlebitis terminating in the formation of clots which sometimes proceed to suppuration and may even produce pyemia; in other instances organization of the thrombus occurs. Such cicatrized areas may constitute tags, or flaps, or even polypoid masses. The venous stasis, and consequent capillary congestion, are frequently attended by hemorrhage (*bleeding piles*).

[1] 'Brit. Med. Jour.," Dec. 6, 1902, p. 1764. See also Duckworth and Garrod, "Medico-Chirurg. Trans.," 1901, and "Lancet," March 8, 1901

CHAPTER XI.

LIVER.[1]

Normal Structure and Function.—In a number of ways the liver resembles the mucous membranes in that the connective tissue passing throughout the organ corresponds to the basement membrane, and the cell elements of the lobules to the epithelium; upon the latter the functional activity of the organ depends. The lobules are formed of hepatic cells arranged in rows radiating from a common center. The blood-supply, derived from the portal vein, passes from the periphery of the lobule toward the center; the course taken by the blood from the hepatic artery is of necessity similar, as the blood derived from the two sources finds its exit by the one route—the hepatic vein, which leaves the center of the lobule. Schaffer has approved the view, advanced by Prowicz, that not only do the biliary capillaries arise within the cell, but that there are intracellular nutritive canaliculi; whether these latter structures communicate with the blood-vessels or the lymphatics of the organ is still a matter of doubt, but, in either case, vascular stasis might directly influence the nutrition of the cell and in this way offer an explanation for the marked changes occurring in the hepatic cell as a result of impeded circulation. The existence of intracellular nutritional canals would also afford a histologic explanation for the cell-necrosis observed in various intoxications, as, by such a route, poisons would be brought into intimate contact with the cell protoplasm. The biliary capillaries arise within the lobule and are probably connected with, and penetrate the hepatic cell through the intermediation of minute channels, called intracellular biliary canaliculi. The existence of such spaces enables us to understand why retention of bile, as the result of obstructive disease of the hepatic ducts, exerts such a deleterious influence on the liver cells.

The lobule is the gland unit and the hepatic cell is the cell unit. The gland differs from all other glands in its blood-supply: there is the usual arterial afflux, represented by the hepatic artery; to this is added the portal supply—an enormous volume of blood—brought from the digestive canal, laden with the products of food metabolism. The portal vein is distributed to the periphery of the lobule, and the zone immediately adjacent is known as the *portal vein zone;* in the center of the lobule is the hepatic vein, draining the blood from the lobule, and the tissue immediately surrounding this is known as the *hepatic vein zone;* between the two areas just indicated lies a zone called the intermediate or *hepatic artery zone.* Histologically and physiologically, these zones are not differentiated, but disease processes, as will be seen later, outline them in a more or less well-marked manner.

[1] For information or literature concerning diseases of the liver consult "Nothnagel's Encyclopedia of Practical Medicine," American edition, volume on "Diseases of the Liver, Pancreas, and Suprarenal Glands," 1903. Also Rolleston, "Diseases of the Liver, Gall-Bladder, and Bile-Ducts," 1905.

The lobule is surrounded by connective tissue, which is continuous with that of the median fissure and the capsule, and is known as the capsule of Glisson; in this the portal vein, the hepatic artery, and the bile-ducts ramify, and these carry into the lobule enough of the connective tissue for support. In man the lobule is not sharply differentiated, and a number of lobules often appear confluent. By confluence or juxtaposition many lobules form a lobe, and these lobes constitute the organ. The portal vein, representing the collected blood from the alimentary canal and spleen, is of itself a circulation, in the sense that there is a capillary system at either end. It differs from the other blood systems, pulmonary and systemic, in that, between the two capillary areas—the one in the intestine, stomach, etc., and the other in the liver—there is no propelling body, and the blood must flow, in this subsidiary circulation, by reason of the cardiac force distributed to the capillary system in which the portal vein finds its origin. Pathologically, this is of the greatest importance, for when the general circulation is feeble, whenever there is a tendency to stagnation, to venous stasis, how unfortunately situated is the portal system to escape the inevitable result! When the blood leaves the surface, as in the chill of malaria, and there is a tendency to distention of the veins, those of the portal circulation are most prone to suffer. So it is that diseases of the lung or heart, which impede the onward flow of the blood, particularly in the veins, evince their most marked secondary alterations in the hepatic and intra-abdominal digestive structures.

Physiologists have agreed that the liver performs the following functions:

1. *Hemolytic:* Disorganization of blood elements is necessary to the production of bile coloring-matter, and it is generally believed that this hemolysis is, at least in part, a function of the liver, or is begun in some other organ, as the spleen, and completed in the hepatic tissues.

2. *Secretory:* Bile is not only eliminated by the liver, but is manufactured by the hepatic cells; the importance of this has been considered when discussing the pathology of jaundice (p. 234).

3. *Urea production:* The liver is believed to be an essential factor in the production of urea.

4. *Glycogenic:* Glycogen is manufactured in the liver.

5. *Detoxifying:* The interception and destruction of poisons. This function has been demonstrated with regard to the hepatic action on strychnin, of which the dose by the stomach or injected into the hepatic blood-supply may be much larger and less injurious than similar quantities given by the systemic circulation. Toxicologists also recognize the filtering influence of the liver, in that poisons may be recognized in that organ when not discoverable elsewhere. Viola[1] has shown that in pregnancy the detoxifying function of the liver—by which I mean its poison-neutralizing property—is lowered, and it may be that this in part accounts for the intense structural changes occurring in the organs in the toxemia of pregnancy. (See p. 80.) The experiments of Brunton and Bokenham[2] clearly establish that the toxicity of the poison produced by the diphtheria bacillus is lessened by passage through the liver or contact with the expressed juice of hepatic cells. The modern conception

[1] "Lo Sperimentale," 1902.
[2] "Jour. of Path. and Bact.," Nov., 1904.

of immunity (p. 99) rests upon the hypothesis that poisons are anchored to the cells upon which they act, and the well-known fact that the liver suffers in many intoxications can be adduced as pathologic evidence in support of the view that the organ possesses detoxifying qualities. Padoa[1] has shown that not only does the liver alter toxin, but that the organ, in accomplishing this function, suffers in direct proportion to the amount of toxin which it anchors or transforms. It is generally stated that bile is bactericidal,—usually to a higher degree than the blood,—but the frequency with which the hepatic ducts and gall-bladder are infected shows conclusively that the bacteriolytic activity, like similar functions in other body-fluids or organs, is restricted.

6. *Adipopexic function:* That the liver stores fat and that it may manufacture or at least convert fat is well known. We do not know, however, why, in certain conditions, the fat accumulates in the liver far in excess of the normal, at the same time that other organs and tissues are wasting.

The normal weight of the liver varies from 1200 to 1800 gm. Its relative weight compared with that of the body is slightly less in the female than in the male. According to Verraeck, the specific gravity is about 1.039; in tuberculosis it may be reduced to 1.020; it is raised in cirrhosis. Postmortem the under surface of the liver is usually darkened (**pseudomelanosis**) from contact with the intestine and stomach. Gas-production in the liver (**foam liver** or **emphysematous liver**) is occasionally seen at autopsy. The cavities are usually small; the cut surface resembling a sponge. The condition is usually due to the Bacillus aërogenes capsulatus (p. 135) and occasionally other gas-producing organisms.

Malpositions of the liver may be congenital or acquired; when the viscera are transposed, the liver passes to the left side. The most important forms of malposition are acquired and are classed under the term **hepatoptosis**[2]; mobile liver, floating and wandering liver, are names also used. In anteversion the anterior border passes downward and forward, and the position of the posterior remains unchanged or rises. The oblique displacement consists in prolapse of the left lobe, the right remaining in place or descending slightly. In total displacement the whole organ is affected. Anteversions are relatively frequent, oblique displacements less common, and total prolapse rare. Prolapse is thought by some to favor the development of gall-stones; of the ninety cases of hepatoptosis collected by Judet, cholelithiasis was present in fifteen. Steele has shown that in prolapsed liver the pressure necessary to force fluid through the biliary passages rises. The liver is also displaced by pressure changes on either side of the diaphragm; ascites or large abdominal tumors force the organ upward. Pleural effusion, hydrothorax, and tumors affecting the right pleura or lung, displace the organ downward. Abnormally large livers are supposed to drag upon the diaphragm and sometimes descend without altering their relations to that structure.

Malformations of the Liver.—Rarely the liver is absent; sometimes

[1] "Riv. Crit. di Clin. Med.," Sept. and Oct., 1904.

[2] Judet, "Revue de Gyn.," Paris, 1901, vol. vi. Steele, "Univ. of Penna. Med. Bull.," Jan., 1903, p. 424. Meyer, "Berl. klin. Woch.," 1904, No. 16. Prentiss, "Amer. Jour of Obstet.," May, 1904.

it is miniature, and occasionally the left lobe is the largest. Accessory lobes, or even small accessory livers, occur, and changes in the position and depth of the tissues are not exceedingly rare. Abnormal lobes attached by a pedicle are sometimes found in hernial sacs at the umbilicus; they have been mistaken[1] for tumors and excised. Tongue-like lobes are usually acquired and the result of constriction. The liver is sometimes divided into a large number of irregular lobes; Moser reported a case in which there were sixteen; some such organs are true malformations, but others are due to congenital syphilis. The gall-bladder may be absent, buried in the liver tissue, and is occasionally directed backward instead of anteriorly. The biliary passages[2] are occasionally impervious and sometimes absent.

Hyperemia of the liver is physiologic during digestion, and by some is believed to be a constant condition in diabetes.

Chronic congestion of the liver[3] results from any condition that retards the venous circulation and slows the blood in the inferior vena cava; the most frequent causes of this condition are valvular heart disease (p. 519), especially mitral disease, and pulmonary obstruction, as in emphysema, chronic bronchitis, etc. The retarded circulation raises the pressure in the thin-walled hepatic veins, which, being most distensible within the lobule, gradually dilate, and by pressure, and associated malnutrition, lead to atrophy of the juxtaposed liver-cells; the zone adjacent to the hepatic vein is first affected, and, histologically, may be composed of dilated branches of the hepatic vein, with complete destruction of those hepatic cells lying immediately around the central vessel. The retarded circulation favors the infiltration of fat, and the margin of the lobule may contain such an excess of this substance that it appears distinctly yellow to the naked eye.

Macroscopically, the organ is much larger than normal, and may attain considerable size; that this is largely a vascular distention is shown by the fact that when the veins pulsate, the liver may also manifest this phenomenon. The organ is red, hence the name, **red atrophy,** and, on section, oozes considerable blood; the lobules can usually be made out, and the dark-red center of each lobule, with its lighter periphery, resembles a transverse section of a nutmeg, and hence the name, *nutmeg liver.* In some cases there is considerable increase in the connective tissue. Pigmentation is almost constantly present; the granules are red or brownish, and occupy the liver cells and the endothelium of the capillaries and lymphatics. While the organ during life may be much larger than normal, when removed and drained of blood it shrinks and presents a wrinkled capsule, and is much lighter than its antemortem size indicated.

Occlusion of the hepatic artery[4] or its branches produces necrosis in the liver tissue, although the process is not that of a typical infarction; this is due to the nutrition supplied by the branches of the

[1] Salvia, "Revue de Chir.," Oct., 1902. Tuffier, "Soc. de Chir.," July 22, 1903; "La Presse Méd.," July 25, 1903, p. 540.

[2] Ferguson, "Amer. Med.," Dec. 21, 1901. Wollstein, "Arch. of Pediatrics," March, 1902. Kirmisson and Herbert, "Société Anatomique," March 27, 1903; La Presse Méd.," April 1, 1903, p. 276.

[3] Hart, "Zieg. Beitr.," 1904, Bd. xxv, p. 303. Gèraudel, "La Presse Méd.," Dec. 3, 1904, p. 769.

[4] Tischner, "Virchow's Arch.," 1904, Bd. clxxv, p. 90.

portal vein. In Tischner's experiments sometimes one-third to one-half of the organ was necrotic. According to Grunert,[1] there are thirty-five recorded cases of aneurysm of the hepatic artery. They sometimes cause jaundice by obstructing the bile-duct, and may erode the liver, stomach, or duodenum, and into the last two cavities they occasionally rupture.

Thrombosis of the portal vein[2] is sometimes observed in chronic obstruction, but is usually due to a thrombophlebitis which may occlude one or more branches or the main trunk of the vessel. Thrombosis occasionally results from extension of neoplasms from the stomach, intestines, or pancreas, or from the biliary passages. Infective and suppurative processes involving the spleen, intestine, mesentery, retro-

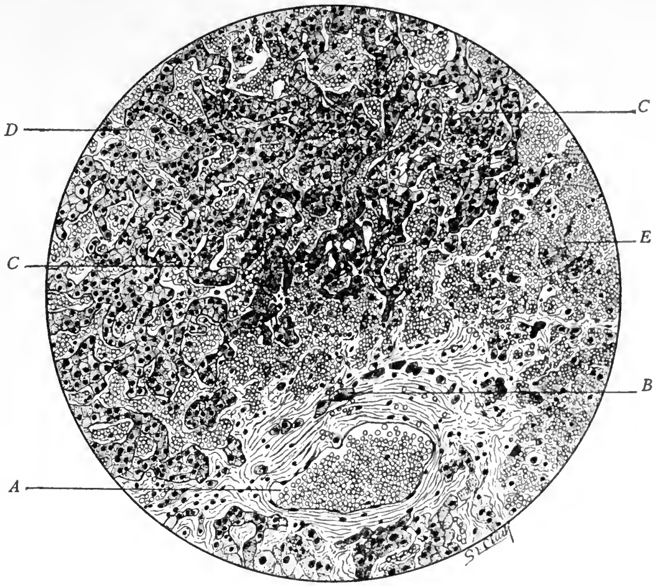


FIG. 361.—LIVER, ADVANCED RED ATROPHY.

A. Central vein the wall of which contains red cells, and at *B* pigmented endothelial cells. *C*, *C*. Columns of liver cells. *D*. Dilated intralobular capillaries distended by erythrocytes. *E*. In this area the columns of hepatic cells have largely disappeared and the capillary walls have wasted or been absorbed.

peritoneal tissues, or bile-ducts, and especially those occurring in the appendicular region, may be attended by thrombosis of the portal vein. The condition is occasionally observed in typhoid; the thrombus may organize, or as a result of infection undergo necrosis; either process may be attended by the formation of emboli which necessarily enter the liver. Where the thrombus gives rise to obstruction, there is not infrequently an intense ascites. In the case reported by Schulz and Müller tapping was necessary every ten to fourteen days. The blood-supply to the liver afforded by the hepatic artery may prevent

[1] "Deut. Zeit. f. Chir.," Dec., 1903.
[2] Steinhaus, "Deut. Arch. f. klin. Med.," 1904, Nos 3 and 4, p. 364. Gerster, "Trans. Amer. Surg. Assoc.," 1903.

any important structural changes in the hepatic tissue. In some cases fibrous hyperplasia and occlusion of the intrahepatic portal branches occur.

Typical **infarction of the liver,**[1] identical with that observed in other organs, is exceedingly rare. Hepatic infarcts may be produced by thrombosis, embolism, or occlusion affecting the portal vein, hepatic artery, or hepatic vein. An essentially similar condition results from laceration of the hepatic tissue with or without rupture of the capsule. Hepatic infarction appears to be more frequent after occlusion of the artery than the vein, and in this form the necrosis is anemic rather than hemorrhagic. The studies of Zahn and Chiari indicate that a form of hemorrhagic infarction called atrophic is most commonly produced by portal embolism, although Steinhaus has shown that it may result from occlusion of the hepatic artery. The areas of necrosis are usually irregular, marginated by a zone of reactionary inflammation and attempts at repair; smaller multiple infarcts give rise to miliary necroses which later are infiltrated by leukocytes, and if not infected, form nodules of fibrous tissue. Some efforts at hepatic regeneration can occasionally be recognized. The suppurative lesions following infarction will be discussed with hepatic abscess. It is evident that embolic phenomena frequently involve the liver without producing necrosis. I have on more than one occasion observed neoplastic emboli in the hepatic tissue when even microscopic necrosis was absent.

Hypertrophy of the liver is infrequent except as a compensatory process. When one lobe or one part of a lobe is destroyed by trauma or disease, increase in the amount of the residual hepatic structure is usually observed; thus, in atrophy of one lobe or a part of a lobe as a result of pressure, or in destruction of one lobe by abscess or cyst, if the patient fully recovers, hypertrophy of the remaining liver tissue may occur. Regenerative effort can often be recognized in the hepatic tissue; it is characterized by proliferation of the hepatic cells in which karyokinetic figures can frequently be recognized. The new cells are rarely assembled in the histologic order of the normal liver.

Atrophy of the liver arises from several causes:

Simple atrophy of the liver, due to starvation or inanition: *e. g.*, in the writer's collection is a liver weighing about 560 gm., taken from a patient who died slowly, from starvation, as the result of cancer of the esophagus. In such cases, associated with general atrophy, the liver may be reduced to one-third of its normal dimensions and weight. The process is probably both simple and numeric, and begins at the periphery, where the evidences are most marked; every part of the organ, however, is implicated.

Morbid Anatomy.—Such a liver possesses a sharp margin, and is darker in color than the normal organ; the relation of lobes, one to another, is normal; after removal from the body and when drained of its blood, the capsule is wrinkled, because the remaining liver-cells no longer fill it; the gall-bladder frequently projects from three to seven centimeters beyond the hepatic margin, The blood-supply to the

[1] Longcope, "Univ. of Penna. Med. Bull.," Aug., 1901. Baldwin, "Jour. Med. Research," 1902, vol. viii. See also Tischner, "Virchow's Arch.," 1904, Bd. clxxv, p. 90; and Steinhaus, "Deut. Arch. f klin. Med.," 1904, Nos. 3 and 4, p. 364.

organ is poor in nutrition, the absence of food from the alimentary canal excludes the normal stimulus to secretion, and, as a result of the combined conditions, very little bile is produced. Histologically, reduction in the size of the lobules is extremely marked; the liver cells are small, atrophied, usually stain indifferently, and are frequently pigmented; there seems to be as much fibrous tissue as liver structure, but this is probably due, not to an increase of fibrous elements, but to a diminution in the size and number of the hepatic cells.

Pressure atrophy of the liver covers a multitude of lesions. Women who lace tightly, by pressing in the margin of the ribs, produce a deep groove or impression in the larger lobe of the liver, and may almost completely divide it; the same result is accomplished in men who wear tight belts, as is so frequently done by certain classes of laborers. The liver is very susceptible to pressure, and is, therefore, influenced by neoplasms in adjacent organs, and by tumors and collections of gall-stones or accumulated secretion or inflammatory matter in the gall-bladder.

Another form of atrophy from pressure is **red atrophy,** which has already been discussed; in this condition the pressure is exerted by the blood retarded in the liver lobule, thus compressing the cells and leading to their disappearance. (See Congestion of the Liver, p. 740.)

A certain amount of atrophy accompanies amyloid infiltration, in that the new deposit in the liver interferes to a variable extent with the function of the adjacent cells. The older view that the evident wasting of the hepatic cells in cirrhosis was due to pressure is no longer insisted upon; the prevailing belief is that cellular necrosis and fibrous hyperplasia are due to the same cause, and that contraction is not an important element in the production of atrophy. Obstruction to the bile-ducts is followed by necrosis of the liver cells, pigmentation of the organ, and atrophy of the parenchyma; the liver not infrequently appears large, but the increased size is due to connective-tissue hyperplasia, swelling, and changes in the bile-ducts. (See Cirrhosis.) Obstructed bile-ducts give rise to pigmentation and atrophy of some of the cells. In all forms of atrophy of the liver more or less pigmentation of the organ is commonly present; besides the pigmentation incident to atrophy, the lesion itself interferes with the production, and may also obstruct the escape of the bile (*acute yellow atrophy*). (See p. 747, also Jaundice, p. 234.)

Infiltrations to which the liver is liable are: (1) Fatty infiltration, (2) amyloid infiltration, and (3) pigmentary infiltration.

Fatty infiltration of the liver arises as the result of an abundance of fat, sugar, or alcohol supplied to the organ; in all of which cases the liver acts merely as a storehouse for the temporary deposit of the nutrient element not needed by the system at large; a certain amount of fat is normal, and is essential to the elaboration of perfect bile. Those causes just cited represent nothing but an excess of the normal.

Fatty infiltration of the liver is also observed in those diseases in which oxidation is in abeyance. As an example of this form may be mentioned the fatty infiltration found in consumption, cachexia, anemia, and allied conditions. The slowed circulation in chronic congestion is probably the cause of the fatty infiltration accompanying the condition. In certain forms of cirrhosis, particularly that due to

alcohol, considerable fat is usually present in the liver lobule, and the color of the organ is largely due to the presence of this body. The lesion produced by phosphorus-poisoning is held by some to be a fatty infiltration, and by others a fatty degeneration; it is possibly a combination of the two processes.

Morbid Anatomy.—The liver of fatty infiltration is sometimes enormously increased in size, and is usually the largest liver seen in the postmortem room; it is firm, the margin rounded, its capsule smooth, pale in color, bloodless, even on section, and when incised with a moist, clean knife, distinctly greases the blade. While the organ may weigh from three to four kilograms, its specific gravity is low, owing to the amount of fat which it contains; the added fat being lighter than water, the

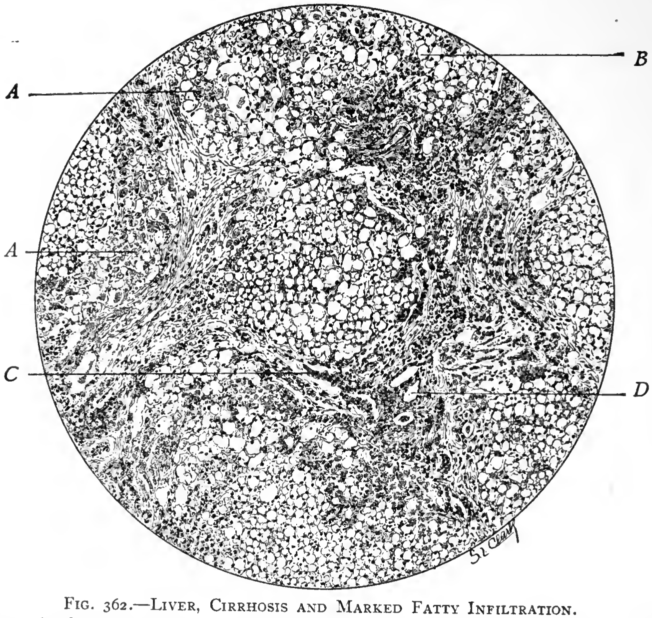


FIG. 362.—LIVER, CIRRHOSIS AND MARKED FATTY INFILTRATION.

Death was the result of croupous pneumonia, and, therefore, an added granular degeneration (cloudy swelling) of the few previously unaltered liver cells is also present. *A*, *A*. Groups of granular liver cells. *B*. Liver cell, the protoplasm of which is almost completely replaced by fat. *C*. Imperfectly outlined bile-duct. *D*. Branch of portal vein surrounded by the newly formed fibrous tissue.

organ may possess a specific gravity of 1000. The gall-bladder does not extend to the margin of the organ; the bile is usually lighter in color than the normal, but clinically there is no evidence, in ordinarily fatty livers, that the bile is deficient in functional activity.

Morbid Histology.—In the earlier stages of fatty infiltration the fat is most abundant in the periphery of the liver lobule, occupying largely the portal vein zone; in extremely advanced cases the infiltrated area may approach the center of the lobule, but not until the margin is extensively invaded. As a rule, the fat exists as a single large globule in the liver cell, crowding the nucleus to one side; the nucleus frequently appears normal in structure and in stain reaction. Liver cells adjoining those containing large quantities of oil are, as a rule

uninvolved; granular or cloudy change in the unaffected cells is rarely present, a fact of considerable value in differentiating the liver cell of fatty infiltration from the same structure in fatty degeneration. (See Fatty Infiltration, p. 224.)

Lardaceous disease of the liver is manifested by an infiltration into the organ of a peculiar body, called lardacein. (See p. 228.) The infiltrated substance is initially deposited in the intermediate or hepatic artery zone of the liver lobule; the causes are those of amyloid infiltration in general.

Morbid Anatomy.—The typic amyloid liver is very much increased in size, its margin rounded, and the capsule smooth and free from thickening; the tissue is firmer and more elastic than normal, contains

FIG. 363.—LIVER, FAIRLY ADVANCED LARDACEOUS DISEASE. (The organ weighed 17 pounds.) *A*. Central vessel of lobule surrounded by considerable residual liver tissue; the periphery of the lobule with corresponding parts of adjacent lobules also persists. *B*, *B*. Lardacein. *C*. Interlobular vessel.

little fat, and is pale and bloodless; the cut surface responds to the chemic and stain reactions commonly given by amyloid material. (See p. 230.) Amyloid infiltration not infrequently involves livers in which other processes militate against great enlargement, or the lardaceous deposit is sometimes scanty and not widely distributed; in either case the organ is not conspicuously enlarged, or often is normal in size; cirrhotic livers containing traces of lardacein may be small.

Properly prepared sections show the lardaceous material more or less irregularly distributed in the intermediate or hepatic artery zone of the liver lobule. The branches of the hepatic artery manifest the usual lardaceous deposit in their walls.

Pigmentary infiltration of the liver occurs in connection with chronic

malaria, and is associated with other lesions that give the organ the name of *malarial liver*. The cause of the process evidently lies in two conditions: (1) The repeated engorgement occurring as a result of the malarial paroxysm, the liver being enormously distended with blood at each chill; and (2) the hematolytic changes, induced by the malaria parasite, liberates the coloring-matter (hemoglobin), which, after important alterations, is finally deposited in the hepatic tissues. The pigment liberated by rupture of the red blood-cell containing sporulating hematozoon is taken up by phagocytic white cells (melaniferous leukocytes, see pp. 191 and 413), which deposit it in the organs. The granules are often found in the endothelial cells of the lymph- and blood-vessels, free in the interstitial spaces, and also within the liver cells. Craig[1] observed melaniferous leukocytes in the capillaries of the liver and also white blood-cells containing bodies resembling degenerated parasites of malaria. As hemolysis is excessive and conversion of blood-pigment into bile imperfectly performed in malaria, the pigmentation may be, in part at least, the result of functional inactivity of the hepatic cell. When the condition has persisted for any length of time, increase in the connective tissue of the organ is sometimes observed. Another form of hepatic pigmentation in which the coloring-matter is derived from the blood is seen in hemochromatosis (p. 234).

In pigmentary infiltrations of the mucous membranes, and especially of the lungs, such as anthracosis, the pigment, entering the blood from lymph-nodes which have ruptured into a vein, reaches the liver and is deposited in the connective tissue that surrounds the hepatic vessels, giving rise to a certain amount of pigmentation of the organ. (See Pigmentary Infiltration, p. 231.)

Morbid Anatomy.—During life, when distended by blood, and when the process is not combined with cirrhosis, the organ is larger than normal; postmortem, it is usually smaller, but the rounded margin and wrinkled capsule indicate that the shrinking has been a postmortem process. Usually, the wrinkled surface can be rendered smooth by stretching. The color, due to the deposited pigment, is grayish-brown or slaty; this grayish, lusterless, lead color justifies the name *slate-colored liver*, sometimes given to the organ. The liver is more or less flabby or flaccid, resists incision more than the normal organ, and, on section, oozes considerable blood and pigmented serum; the gall-bladder is small and does not extend to the margin of the liver; the contained bile is commonly tarry or thick and ropy. Under the microscope a blackish or brownish pigment is found disseminated throughout the organ, around the lobules, and in the perivascular intralobular structures; this is altered blood coloring-matter (melanin). Associated with the pigment deposit a considerable increase in the connective tissue is usually observed; this may be so great as to constitute an actual cirrhosis; the newly formed connective tissue is found not only in the interstitial structures around the lobules, but in the intralobular reticulum as well.

The foregoing description applies particularly to the hepatic enlargement of chronic malaria. If death occur early in the infection, pigmentation is, of course, less marked. The malaria parasites may be present in the organ, particularly in the estivo-autumnal fever.

[1] "Amer. Med.," July 25, 1903, p. 145.

Necrotic areas associated with, or independent of, capillary thrombosis are occasionally observed.

The degenerations most frequent in the liver are parenchymatous and fatty.

Parenchymatous degeneration of the liver is found in connection with high temperatures, septic and other infectious processes, and in many intoxications. (See p. 241.) The organ is swollen, is usually pale, and the cut surface is cloudy and opaque, not shining and translucent, like the normal; with the granular change in the epithelium of the lobules there is not infrequently more or less necrosis, usually coagulative in character. The bile elaborated by such an organ is deficient in quantity and may be physiologically inert. The affected liver-cells are granular (Fig. 140, p. 242) and show the initial changes observed in the first stage of fatty degeneration. By some it is believed that the structural alteration is essentially similar to that of beginning catarrhal inflammation of the lobule, analogous to the lesion observed on the mucous surfaces in the stage of catarrhal inflammation when desquamation is impending; the belief that the degenerative and necrotic changes constitute a part of an inflammatory process has led to the condition under consideration being called **parenchymatous hepatitis.** The process is of a type justifying the conviction that it is inflammatory, and in some respects more closely resembles the necroses; like the latter, it may be appropriately regarded as a sequence of the toxic action of poisons brought to the liver by the circulating blood.

Acute yellow atrophy of the liver,[1] also known as *malignant jaundice, icterus gravis, essential hemorrhagic icterus, and acute fatty degeneration* of the liver, are names applied to an obscure affection about the etiology of which we are in doubt. The exact character of the changes observed also remains undetermined; Taylor's studies indicate that, at least in some cases, the fat-content of the organ is not increased, and that, therefore, it is not a fatty degeneration. Many who investigated the condition believe that it is primarily a necrosis, and with this view I am inclined to agree. The name acute yellow atrophy is noncommittal, describes the common anatomic manifestations, and does not indicate the process by which the change occurs.

The cause of this condition is not known, but the feeble tendency to epidemicity, and the fact that the etiologic agent attacks individuals in groups,—among pregnant women many cases may occur in a single locality,—taken with the character of the symptoms and lesions, indicate a possible infectious agent. A similar condition has been produced in animals by bacterial toxins, and bacteria are frequently observed in the affected organs. I believe all investigators agree that the disease is of toxic origin, although unanimity as to the character and source of the toxic body is wanting. It has been observed after chloroform anesthesia, particularly in children, but Guthrie believes that some antecedent condition determines its occurrence and that it is not directly

[1] MacCallum, "Johns Hopkins Hospital Reports," 1902, vol. x. Taylor, Jour. of Med. Research,' 1902, vol. viii, p. 424. Guthrie, "Lancet," Jan. 27 and Feb. 3, 1894, pp. 193 and 257, and "Lancet," July 4, 1903, p. 10. Cohn, "Zentralbl. f. Gynäk.," Oct. 8, 1904, No. 34. De Paoli and Pietro, "Arch. f. Gyn.," 1904, Bd. lxxiii, p. 357. Wells and Bassoe, "Jour. Amer. Med Assoc.," March 4, 1905, p. 685.

the result of the anesthetic. The disease is most common in women, especially during the puerperium, and usually occurs between the ages of twenty and thirty. As before stated, the changes induced by phosphorus and arsenic are analogous, but not always identical. Some observers are inclined to regard the process as inflammatory; others, as a purely degenerative change secondary to necrosis of hepatic tissue produced by a poison the exact nature of which is unknown.

Morbid Anatomy.—In typic cases the organ is much reduced in size and weight, is flabby, and, when the change is advanced, can be folded over upon itself; as a whole, the consistence may be almost that of a bag of fluid—semifluctuating; the capsule is wrinkled. The color is not uniform; on the surface and on section dirty yellow areas, varying in size and irregular in form, are often conspicuous; around and between these patches the liver is red, cloudy, and frequently distinctly firmer. While the organ occasionally resists incision, the semifluid condition of its contents is shown by the fact that large quantities of hepatic tissue may be extruded through a small opening. There may be hemorrhage into the organ, although this is more common in other viscera than in the diseased liver. The myocardium is usually soft, granular, or fatty, and hemorrhages into the muscle or beneath the pericardium or endocardium are usually present. Necroses and infarction are common in the spleen; the renal epithelium is usually granular or fatty, and desquamating, and sometimes a marked acute diffuse nephritis is present.

Under the microscope the changes to be observed are most intense in the yellowish areas already described. The liver-cells are indistinct in outline and often extremely fatty; all stages of fatty degeneration are recognizable; cloudy and granular cells and cells containing minute oil-globules abound, and occasionally areas occur in which the cells are no longer demonstrable. The fat seen in the liver cell is both within and around the nucleus, and sometimes exists as minute granules or oil-globules, in contradistinction to the large drops usually present in fatty infiltration; these differentiating points, however, are not trustworthy. The evidences of nuclear fragmentation and cell-necrosis are not present in simple uncomplicated fatty infiltration. All zones of the liver lobule are invaded in rapid succession, apparently the outer or portal vein zone first. In some cases the connective tissue between the lobules is normal; in others it shows a tendency toward proliferation.

Coagulation necrosis, as seen in the liver, occurs in typhoid fever, diphtheria, and allied infectious processes. It can be produced by bacterial toxins, especially those of the diphtheria bacillus, and by abrin and ricin. Boxmeyer[1] has studied the hepatic necroses produced by hog-cholera bacilli, and concludes that the lesions are of two kinds: one is produced by plugging of the capillaries by large mononuclear cells and the direct action of the toxin; the other results from hyaline thrombi in the smaller veins. Pearce[2] suggests that thrombi may result from agglutinins within the blood—the agglutinin thrombi originally described by Flexner. Opie,[3] in studying necrosis within the

[1] "Jour. of Med. Research," March, 1903, p. 146.
[2] "Albany Med. Annals," Dec., 1904.
[3] "Jour of Med. Research," July, 1904, p. 147.

liver lobule, found that they might be central, peripheral, or in the mid-zone. The periphery of the lobule was the least frequently affected. The hepatic necroses accompanying eclampsia[1] are regarded by many observers as the most constant lesions of the disease. Prolonged blood stasis, infarction, injury, biliary obstruction, and direct infection of the hepatic tissue give rise to necrosis. The **focal necroses** include those due to bacterial toxins, and occur in organs already the seat of cloudy swelling; the necrotic areas are minute, white or yellowish-white in color, cloudy, and opaque. Histologically the liver cells rapidly disappear and are replaced by a hyaline matrix in which are fragments of nuclei and homogeneous, degenerated, or necrotic protoplasm. Little is known with regard to the ultimate fate of these areas in patients who recover. Reed has described fibroid nodules that could have had such an origin, and a number of investigators have suggested that the condition might give rise to cirrhosis. In eclampsia, in addition to the necrosis, minute hemorrhages are usually present.

Hepatitis (inflammation of the liver), like nephritis, does not yield itself to systematic classification. By some observers the conditions called cloudy swelling and acute yellow atrophy are classed with inflammations of the organ and constitute different phases of what is termed **acute parenchymatous** or **nonsuppurative hepatitis.** Klein described an acute inflammatory affection of the liver analogous to acute diffuse nephritis, and Remlinger, Jaboulay, and others speak of an acute swelling of the liver associated with splenic enlargement which they call **acute infectious liver.** Of these conditions our information is too indefinite to justify specific statements as to their essential nature, etiology, or pathology. Clinically and anatomically we may recognize—(1) suppurative inflammations of the liver and (2) chronic processes attended by the production of an excess of fibrous tissue and ordinarily called cirrhoses.

Suppurative hepatitis or **hepatic abscess** may be acute or chronic and results from bacteria entering—(1) from contiguous structures, (2) by the portal vein, (3) by the hepatic artery, (4) by the biliary channels; (5) traumatic abscess, the path of infection being uncertain, and (6) amebic abscess, in which the causative factor (amebæ) probably enters the liver by the portal vein; the distinctive etiology and pathology justify a separate consideration of this lesion. The suppurative lesions due to infection by the portal vein and hepatic artery may conveniently be considered together as metastatic abscesses. Ulcers and carcinoma involving the stomach may penetrate and infect the liver, producing a slowly advancing suppurative lesion which forms the base of the ulcerative process. Abscess beneath the diaphragm, empyemata, and perinephric suppurations occasionally extend into the liver. Fish-bones, pins, needles, and other foreign bodies may penetrate the liver from the stomach, duodenum, or colon.

Metastatic abscess due to infection, primary in the portal area, results from a pylephlebitis (p. 741) in which pyogenic bacteria are present. Such abscesses are practically always secondary to primary suppurative processes involving the intestine, appendix, rectum, pelvic viscera, or spleen. Rolleston states that such infection is most frequent in

[1] Gilman, "Boston Med. and Surg. Jour.," March 30, 1905, p. 367; also Ewing "Amer. Jour. of Obstet.," Feb., 1905.

appendicitis, and Thompson found portal infection in 29 of 669 autopsies following appendicitis. In such cases the liver practically always contains abscesses, which are not invariably of the same size or age, and, in the latter instance, represent succeeding embolisms. The abscess cavities are most numerous in the right lobe; the condition is usually fatal. When the infection is embolic by way of the hepatic artery, the emboli are usually smaller, the distribution wider, the number of abscesses greater, and each pus collection usually minute, sometimes microscopic. As this form of hepatic suppuration usually accompanies pyemia, the lesions are called **pyemic abscesses.** When such a collection attains a recognizable size, it is usually from confluence of adjacent foci. The affected liver is enlarged, cloudy, and hyperemic; in typical cases the abscesses may resemble miliary tubercles (miliary abscess of the liver), but are soft, and the extruded pus is unlike the caseous material occurring in tuberculosis. Rarely the abscess is large. The collections of pus, when the infection results from thrombophlebitis, are usually larger, probably because the emboli are grosser, or propagation in the intrahepatic branches of the portal vein occurs more readily than in the hepatic artery.

Hepatic abscess may be secondary to infection traveling by the bile-ducts, usually a suppurative cholangitis, which will be found described under Diseases of the Biliary Passages. The abscesses are multiple and are often difficult to differentiate from the metastatic form. Usually the pus is more intensely bile stained, and when sections of the hepatic tissue are examined microscopically, it can be observed that the infection, in the smaller abscesses, has extended from the bile-ducts. The difficulty in identifying the processes is further increased by the fact that abscesses from other causes may penetrate the ducts and give rise to a suppurative cholangitis, which in turn may induce new centers of suppuration.

Traumatic abscess of the liver results from injury, either direct or by transmitted force; blows on the abdominal wall, falls, bumper, and similar accidents induce subcapsular or deeper lacerations in the organ, and these afford opportunities for the colonization of bacteria brought to the liver by the blood. Cysts, quiescent gummata, and tuberculous nodules, or obsolescent areas of old infection, readily suppurate when injured. Traumatic abscess is usually solitary, and at most but two or three foci are found. The pus is frequently loaded with bacteria, commonly bile stained and sharply demarcated from the contiguous liver tissue, which, however, is the seat of more or less reactionary inflammation. Hepatic suppuration due to injury is usually situated in the right lobe near the superior surface. When the lesion is due to penetrating wounds, the position of the injury determines the location of the abscess.

Amebic abscess of the liver[1] is practically always a complication of dysentery; a few reported instances in which the dysentery apparently followed the abscess, or was absent, must be supported by further observation before we are justified in concluding that this form of hepatic abscess arises independently of intestinal amebiasis. The condition is so much more frequent in hot than in temperate climates that it

[1] See references to Dysentery, p. 726; description of amebæ, p. 181; also Rolleston, "Diseases of the Liver," 1905, p. 120.

is sometimes called **tropic abscess.** In about seventy-five per cent. of the cases the abscess is solitary; two are present in ten per cent., and more than two in fifteen per cent.; seventy-five per cent. to eighty per cent. of the abscesses are situated in the right lobe. It has been suggested that the infection is transperitoneal,—that is, through the peritoneal cavity; but if such were the usual route, abscesses in other organs—for example, the spleen—ought to be more frequent, and, besides, this does

FIG. 364.—MULTIPLE AMEBIC ABSCESS OF LIVER. (One-half natural size.)
A. Diaphragm. *B*, *B*. Points of necrosis in liver tissue. *C*. Necrotic wall of an abscess extending into diaphragm. *D*. Disappearing septum between two juxtaposed abscesses.

not account for the deep location of the abscess, and, in addition, transportation of the amebæ by the portal blood seems much more reasonable. The abscesses vary in size from small cavities 2 cm. or 3 cm. in diameter to large collections around which the right lobe forms a thin shell from a few millimeters to a centimeter in thickness. The material contained within the abscess is composed of necrotic fragments of hepatic tissue,

granular detritus, amebæ, and relatively few leukocytes. In the smaller abscesses before liquefaction is complete the necrotic material is thick and viscid and often will not flow through a medium-sized cannula. The wall of the abscess is composed, on the inner surface, of necrotic liver cells and shreddy projections of residual connective tissue; masses of fibrin can usually be recognized. The liver cells beyond the zone of actual necrosis are greatly flattened and distorted, and some are necrotic; within this zone small areas of hemorrhage can sometimes be seen. The absence of polymorphonuclear leukocytes, or, at most, the small numbers present, show that the process is not suppurative in the ordinary interpretation of the term. Bacteria may be present, and it is quite possible for an amebic abscess to be secondarily infected. While

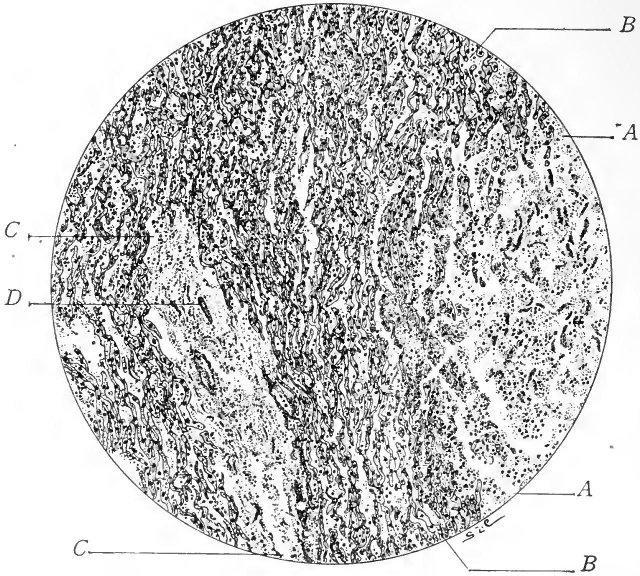


FIG. 365.—LIVER, WALL OF AN AMEBIC ABSCESS. (Fixed in Bensley's fluid; paraffin; eosin and toluidin-blue.) *A, A.* Abscess containing detached and fragmented hepatic cells and cellular detritus. *B, B.* Hepatic tissue marginating the abscess cavity; the inner margin of this zone is composed of necrosing liver cells; the adjacent columns of cells are compressed and distorted. *C, C.* Area of periportal tissue showing considerable edema and necrosis and slight cellular infiltration. *D.* Bile-duct.

other forms of hepatic abscess frequently give rise to embolic processes and metastatic foci in other organs, the amebic abscess rarely does so. Kartulis[1] reports a case of secondary brain abscess in which the amebæ were identified.

The course of developed hepatic abscesses varies. Over fifty per cent. of those that are solitary rupture through the diaphragm, and the larger number of these penetrate the lung and discharge into a bronchus. About twenty per cent. rupture into the peritoneum. Few become encapsulated and assume a quiescent stage. The remainder are evacuated through the stomach, intestines, kidney, bile-passages, or externally; Flexner reported an amebic abscess that ruptured into the vena cava.

[1] "Centralbl. f. Bakt.," Dec. 12, 1904, p. 527.

Chronic interstitial hepatitis, or **cirrhosis of the liver,** is a chronic productive lesion characterized by the formation of fibrous tissue, which, in some instances, contracts. The varied pictures presented by the dissimilar manifestations of cirrhosis, and different conceptions as to its origin, permit of extremely complex classifications, many of which include forms that cannot be identified by clinical methods at present at our disposal. It is clear that the structural changes observed are the result of some form of irritation, and that in one class of cases the irritant enters the organ by the portal system and that in another group the deleterious action is exerted by way of the biliary passages. There is no anatomic or clinical group of cases that would justify a belief that a special form of cirrhosis resulted from the action of an irritant brought to the liver by the hepatic artery; attempts to establish an arteriosclerotic cirrhosis of the liver have not been convincing. There remain, however, the two groups to which I have referred; the first may be called **portal cirrhosis** and the second **biliary.** The former may be further subdivided into—(1) a type characterized by contraction and marked induration, called atrophic cirrhosis, and (2) a form in which the organ remains large and is the seat of a concurrent intense fatty infiltration—fatty cirrhosis. The biliary cirrhosis can be further divided into—(*a*) a form due to obstruction of the larger bile-ducts—obstructive biliary cirrhosis; and (*b*) the hypertrophic cirrhosis of Hanot.[1] In addition to the lesions mentioned there is a chronic hyperplastic process affecting the hepatic capsule, which becomes enormously thickened, giving rise to a condition called capsular cirrhosis.

Atrophic cirrhosis[2] of the liver is also known as *fibroid liver*, *granular liver*, *gin-drinkers' liver*, *hob-nail liver*, *contracting* or *contracted liver*, *chronic interstitial cirrhosis*, *venous cirrhosis*, and *Laënnec's cirrhosis*. According to White, alcohol is accredited with sixty per cent. of the cases of atrophic cirrhosis; but the experimental production of cirrhosis in animals by the administration of alcohol by either the stomach or portal vein has not been conclusive. It is possible that the gastro-enteric catarrhal and fermentative conditions occurring in alcoholics have something to do with the production of cirrhosis. Syphilis is responsible for some cases; rickets, red atrophy, malaria, and infectious diseases are also etiologic factors in the production of the condition. The increased fibrous tissue observed in chronic congestion, malaria, and chronic infections rarely attains the magnitude seen in typic atrophic cirrhosis. It is probable that more than one toxic condition, or at least that a number of poisons, may so irritate the liver as to produce an increased quantity of fibrous tissue. There has been much discussion as to whether the fibrous hyperplasia is primary or secondary; recent investigation indicates that the initial change is a necrosis affecting the

[1] Those interested in a more detailed classification of the cirrhosis should consult Rolleston, "Diseases of the Liver," 1905, p. 174. Edwards, "International Clinics," vol. ii, twelfth series. Also Ascoli, "Deut. Arch. f. klin. Med.," Bd. lxxi, H. 4 and 5.

[2] Vaughan, "Jour. Amer. Med. Assoc.," Oct. 5, 1901 W. Hale White, "Brit. Med. Jour.," March 7, 1903, p. 533. Bleichroder, "Virchow's Arch.," vol. clxxvii, No. 3. Klippel and Lefas, "Rev. de Med.," Jan 10, 1903. Joannovics, "Wien. klin. Woch.," July 7, 1904, p. 757. Kretz, "Centralbl f. allg. Path u. path Anat.," Dec. 31, 1904, p. 985.

periphery of the lobules, and that this is followed by fibrous overgrowth (see Productive Inflammation, p. 297) and other reparative efforts.

Morbid Anatomy.—In atrophic cirrhosis of the liver the organ is diminished in size, not infrequently weighing less than one kilo; the surface is uneven, irregular, granular, or hob-nailed; the tissue is unusually firm and semielastic, and offers considerable resistance when incised; it may creak under the knife. In typic cases the liver is pale yellow, but if jaundice has been present, it may possess something of an orange tinge or be green or greenish-yellow. An intercurrent red atrophy is sometimes present, in which case the usual pallor is obscured by the abnormal amount of blood present. The capsule is frequently thickened and occasionally is adherent to the diaphragm; adhesions when present are abnormally vascular and rarely firm. The gall-bladder is usually slightly diminished in size, the wall, particularly in the serous coat, is frequently thickened. The bile may appear normal, but is frequently watery and dark; in other cases it is thick and ropy. The incised surface is traversed by grayish, often semitranslucent lines or coarser bands composed of the newly formed fibrous tissue. In the presence of intercurrent red atrophy, the connective tissue may be red, but is practically always lighter in color than the hepatic cells which it surrounds. From the coarse bands finer projections can usually be traced around the lobules.

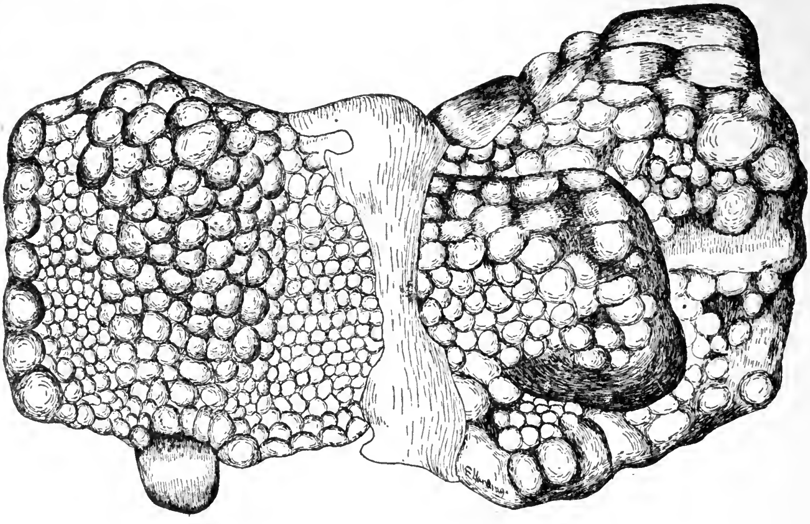


FIG. 366.—SUPERIOR ASPECT OF LIVER, SHOWING UNUSUAL DEGREE OF CIRRHOSIS WITH "HOB-NAILED" SURFACE. *A*. Gall-bladder. The patient was a chronic alcoholic and died from gastro-esophageal hemorrhage. (Illustration one-half natural size.)

The most striking histologic change is the enormous increase in fibrous tissue. The distribution of this substance has been used as a basis for certain anatomic subdivisions; when the bands enclose a number of contiguous lobules the condition is called **polylobular cir-**

rhosis. In the **monolobular cirrhosis** the tendency of the intercalated fibrous elements is to surround and isolate each lobule separately. Usually both types can be recognized, although one may predominate. The fact that the fibrous tissue is around the lobule rather than in it has led to the designation **perilobular cirrhosis** or **interlobular cirrhosis.** When the fibers extend between the columns of liver cells forming the lobule, the condition is called **intralobular cirrhosis**; this form is more common in the hypetrrophic and obstructive types of cirrhosis. The extent of the fibrillation in the newly formed tissue is largely determined

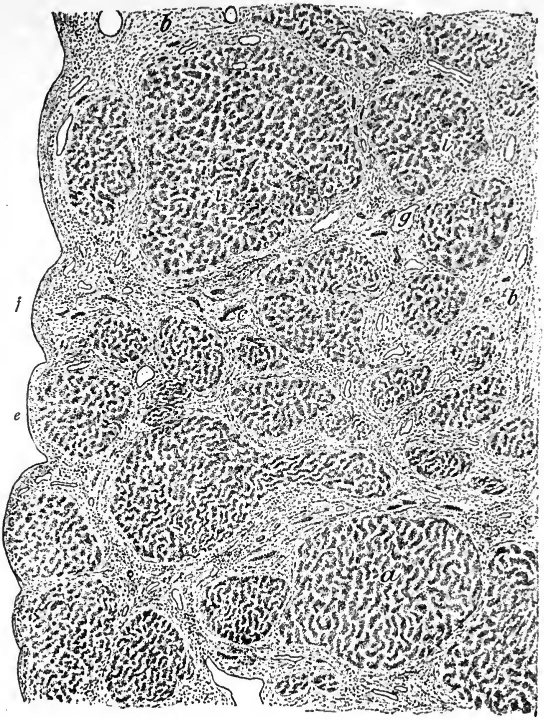


FIG. 367.—ATROPHIC CIRRHOSIS OF THE LIVER, ADVANCED.—(*Schmaus.*) × 50 diameters.
a. Liver lobule. *b, b.* Newly formed fibrous tissue. *c.* Bile-ducts. *d, e, f.* Granules or hob-nails on the surface, of the liver, due to contraction of the newly formed connective tissue. If the masses are small, they appear on the surface of the organ as granules: if large, they form hob-nails. *g.* Branch of portal vein. *i.* Hepatic vein in center of lobule.

by its age. In the more recent stages the interstitial increase is composed largely of mononuclear cells. Later these can be seen forming fibrous tissue, and when the lesion is advanced, the thick cicatricial bands are often nearly acellular. As long as the lesion is progressing, however, mononuclear cells are present in the more recent areas, usually adjacent to the receding lobules. The studies of a number of observers show that the new tissue often contains elastica in varying amounts; this substance, however, is not invariably increased, as I have examined a specimen of advanced cirrhosis in which there is no manifest produc-

tion of elastic tissue. Often columns of cuboidal cells suggesting new bile-ducts are present in the interstitial tissue. It is possible that these structures are due to regenerative efforts on the part of the liver cells; their exact nature, however, is still a matter of doubt. In some forms of cirrhosis, yellowish or brownish granules of pigment are found in the new tissue and in the liver cells. In most cases the granules are derived from the erythrocytes as a result of hemolytic processes. The pigment in **cirrhosis anthracotica** is of extraneous origin (exogenous), and has reached the liver by the blood (see p. 232).

The portal vein and its branches are dilated, the large vein of the round ligament is often conspicuous, and sometimes dilated veins are seen beneath the skin, around the umbilicus, constituting the so-called caput medusæ. The gastric and esophageal veins may be varicose, and, by rupturing, sometimes give rise to fatal hemorrhages. The spleen is moderately enlarged, the capsule frequently thickened, and sometimes adherent to contiguous structures; there is some doubt as to whether the splenic enlargement is due to venous stasis alone or is the result of toxemia. Klippel and Lefas have recently studied the notable sclerosis of the pancreas often associated with contracting liver; in some cases the production of fibrous tissue in the interior of the pancreas is most marked. In the earlier stages, and later when edema is present, the organ may be enlarged. The intestinal mucosa shows the results of chronic congestion, and catarrhal inflammations of the intra-abdominal alimentary canal are frequently present. Ascites occurs in fifty per cent. of the cases; it is usually attributed to the heightened venous tension resulting from portal obstruction within the liver, but may also be due to thrombosis of the portal trunk or of its intrahepatic branches, toxemia, peritoneal irritation, and cardiorenal changes. Jaundice with atrophic cirrhosis occurs in less than one-third of the cases; it is rarely marked, and is usually transient.

Fatty Cirrhosis.—In addition to the increase in the connective tissue observed in atrophic cirrhosis, there may be more or less fatty infiltration, giving rise to an organ that but little resembles the preceding.

Morbid Anatomy.—The fatty cirrhotic liver is large and is usually smooth, but may be slightly granular; as a rule, the surface is undulating and distinctly yellow in color; the organ possesses the rounded margin and general rotundity already noted as present in fatty infiltration (see p. 743; also examine Fig. 362, p. 744); on section, however, it is very much firmer, and contains an excess of fibrous tissue as well as of fat; the fibrous tissue is distributed in the same manner as in atrophic cirrhosis, and with the same result, except that the extensive infiltration of fat enlarges the organ. The fibrous tissue is not so abundant and commonly is structurally immature. The venous obstruction is usually less, and the alterations in other organs are not so marked as when contraction is conspicuous. In my experience this form of cirrhosis is more likely to be latent, often gives rise to no symptoms, and frequently reaches the autopsy table undiagnosed.

Obstructive biliary cirrhosis[1] results from increased pressure within the bile-ducts, although it is evident that some additional factor is neces-

[1] Ford, "Amer. Jour. Med. Sci.," Jan., 1901. Weber, "Trans. Path. Soc of London," 1903, vol. liv, p. 103. Pick, "Wien. klin. Woch.," April 23, 1903, p. 493.

sary, as duct obstruction may be complete and long continued without producing typic biliary cirrhosis. Retention of bile within the liver often gives rise to necrosis of the hepatic epithelium and a productive inflammation around the finer biliary channels. The causes of duct obstruction will be considered with the biliary passages.

Morbid Anatomy.—In the earlier stages the liver is greatly enlarged, but later contracts. During the period of enlargement the organ resembles the liver of typic hypertrophic cirrhosis. Often the dilated ducts can be seen through the capsule; adhesions to contiguous structures occur. The liver resists incision, is intensely bile stained, the surface uneven or granular, and rarely bossed; in the latter case it resembles the hob-nail liver. The incised surface discloses transverse and oblique, less frequently longitudinal, sections of dilated bile-channels, the walls of which are manifestly thickened. The distribution of the fibrous tissue is less uniform than in atrophic cirrhosis, and its cellular character, during the stage of enlargement, is like that seen in hypertrophic cirrhosis. Histologically, the new tissue is both interlobular and intralobular; the larger fibrous masses follow the lines of dilated ducts, but are also projected around the walls of biliary canals in which dilatation is inconspicuous. In some cases focal necroses are abundant, and degeneration of the hepatic epithelium is advanced; the former condition is absent more frequently than the latter. Ascites in obstructive biliary cirrhosis is rare. The fact that the spleen is not greatly enlarged, and that venous distention is inconspicuous or absent, indicates that but little vascular obstruction is present. The most disastrous termination of these cases results from pyogenic infection of the dilated channels and wide-spread suppurative cholangitis, with multiple abscesses along the course of the infected ducts.

Hypertrophic biliary cirrhosis,[1] sometimes called *biliary cirrhosis*, or simply *hypertrophic cirrhosis*, is characterized by marked enlargement of the liver and spleen, the absence of ascites, and the presence of an intense and protracted jaundice; occlusion of the larger ducts is absent. As the liver is enlarged in obstructive cirrhosis, fatty cirrhosis, and sometimes in the earlier stages of atrophic cirrhosis, the use of the unqualified term hypertrophic should be suppressed, and as the obstructive cirrhosis is clearly of biliary origin, the use of the term biliary cirrhosis without qualification gives rise to confusion. The cause of the condition is quite obscure. It frequently occurs in the young, and there are recorded instances suggestive of hereditary influences. The evidences of inflammation in the smaller biliary canals has suggested an infectious origin, although no specific organism has been isolated. If due to bacteria, the location of the lesion must be taken as an evidence of a descending cholangitis.

Morbid Anatomy.—The organ is large, much darker than the preceding varieties, and of a greenish-yellow color; the surface is smooth, the margin rounded, the gall-bladder retracted, and the tissue is firm and offers marked resistance to incision. The cut surface is usually pigmented and bile stained, and the newly formed connective tissue can be seen widely distributed among the lobules.

There is an abundance of mononuclear or oval cells between the

[1] The literature is quoted in full by Rolleston, "Diseases of the Liver, Gall-bladder, and Bile-ducts," 1905.

lobules, and even extending into the tissue of the lobule. The bile-ducts appear to be increased in size and number, and the grouped ducts sometimes form adenoma-like aggregations. By reason of the absence of contraction there is little obstruction to the portal circulation, and hence there is no dropsy. The increased interlobular proliferation and swelling probably obstruct bile-ducts, and in this way give rise to the jaundice. The spleen is notably enlarged, weighing between 400 gm. and 1000 gm., and in rare cases weighs more than the liver. Fibrous changes have been observed in the pancreas. All the body tissues are intensely bile stained. About ten years ago Gilbert and Lereboullet[1] called attention to clubbing of the fingers in hypertrophic biliary cirrhosis; it is said that this manifestation occurs in no other form of hepatitis.

Pseudocirrhosis,[2] also called *hepatic capsulitis*, *perihepatitis*, and capsular cirrhosis, is probably a form of chronic serous membrane inflammation—a chronic hyperplastic hyaloserositis (p. 473)—and should not be grouped with the cirrhoses. Local capsular thckenings are without clinical significance, and it is only when the liver is practically covered by a thick stratum of condensed hyaline fibrous tissue, giving rise to contraction, that the condition becomes important. Rolleston differentiates it from perihepatitis by the fact that the new tissue is beneath the capsule; other writers do not make the distinction. The surface of the organ is covered by hyaline fibrous tissue ("Zuckergussleber," iced liver) which resists incision; sometimes there is a slight cirrhosis, but never the changes of the typic chronic interstitial hepatitis. Vascular distention and wasting of the epithelium (red atrophy) are usually present. Pericardial adhesion and thickening of the splenic capsule are also observed; ascites is sometimes marked.

Syphilis of the liver[3] may result from either congenital or acquired infection. In **congenital syphilis** three important structural alterations are to be recognized: (1) extensive intercalation of fibrous tissue between the lobules, but extending into and around the cells (*pericellular cirrhosis*). This may be diffuse, involving all the organ, or restricted to definite paths which possibly correspond to the distribution of the vessels. The hepatic cells, within the areas of fibrosis, are usually shrunken and often necrotic. (2) *Miliary gummata*, consisting of small collections of lymphoid cells in which stellate or sharply defined giant cells are occasionally observed. In many cases the diffuse lesion, first described, is concurrent with the development of almost microscopic granulomata. (3) Gummata, corresponding to the usual type of syphiloma, occasionally occur in congenital syphilis; they are, however, infrequent. By contraction, the diffuse pericellular cirrhosis may diminish the size of the liver, or, what is more common, the fibrosis—either pericellular or multilobular—follows irregular paths through the organ, and, when it contracts, divides the liver into many lobes—the *polylobulated liver of congenital syphilis*. With regard to the hepatic lesions of acquired syphilis, especially during the secondary period, we

[1] See "Gaz Hebd. de Méd. et de Chir.," 1902, Nos. 1 and 2, p. 1.
[2] See second foot-note, p. 472; also Schupfer, "Rif. Med.," March 2, 1904.
[3] Erdmann, "Deut. Arch. f. klin. Med.," 1902, Bd. lxxiv, H. 5 and 6. Stockton, "Jour. Amer. Med. Assoc.," Nov. 8, 1902, p. 1167. Boix, "Arch. Gen. de Méd." Paris, 1903, vol lxxx, Nos. 19, 20.

possess but little accurate knowledge. The fact that jaundice and hepatic enlargement occur, and that later cirrhosis may develop, indicates the possibility of an acute diffuse interstitial hepatitis and catarrhal cholangitis. Later syphilitic infection gives rise to definite gummata (p. 179). These may occupy the interior of the organ, present on the surface as definite bosses, or rarely as semipedunculated masses. The margin of the gumma is not sharply defined, and, as Birch-Hirschfeld observes, the mass can seldom be shelled out of the hepatic tissue; even in the pedunculated syphilomata liver tissue is present in the

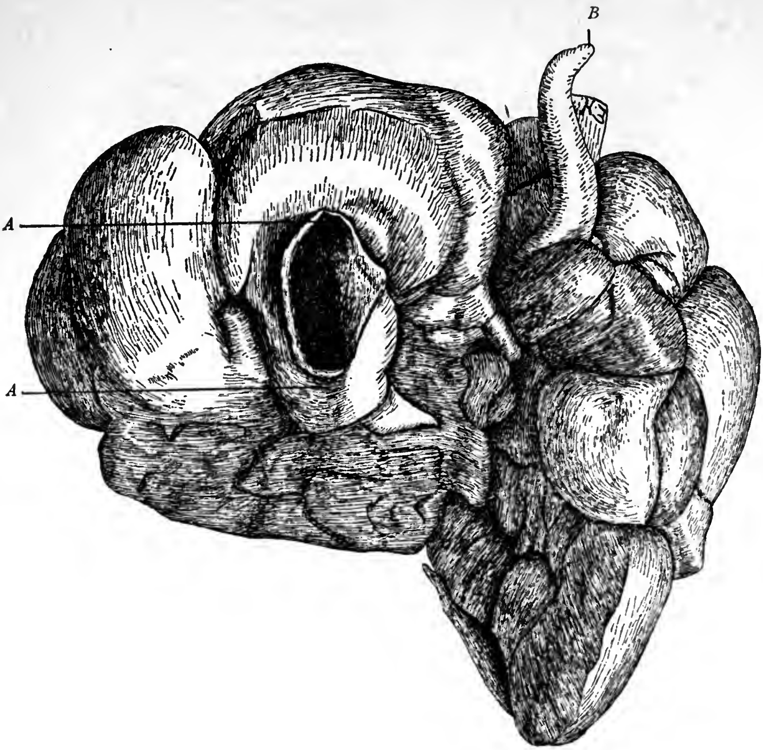


FIG. 368.—UNDER SURFACE OF LIVER SHOWING RESULTS OF CONGENITAL SYPHILIS.

A, *A*. Gall-bladder. *B*. Round ligament. The organ is irregularly fissured in many directions, giving rise to a large number of lobes. The patient from whom this liver was removed died in the second week of typhoid fever; age, seventeen years.

pedicles and partly incloses the nodule. Scars from healed gummata may sometimes be observed. It is well known that syphilitics are subject to amyloid disease, and that this affection commonly involves the liver (p. 227).

Tuberculosis of the Liver.[1]—Pulmonary tuberculosis is often accompanied by fatty infiltration of the liver, with which, or independently, a periportal cirrhosis sometimes occurs. It is known that the poison

[1] Mousset and Bonamour, "Rev. de Méd.," April, 1904. Vincenzo, "Rif. Med.," Nov. 16, 1904. Giordano, "Rif. Med.," Nov 16, 1904.

of the tubercle bacillus sometimes manifests a sclerogenous quality, and it is possible that some of these forms of cirrhosis are due to the action of the bacillary toxins brought to the liver by the circulating blood. Tuberculosis of the liver may be primary or secondary; the former is exceedingly rare. Infection may occur by the portal blood, hepatic artery, lymphatics, or by contiguity; the hematogenous routes are the usual paths by which the bacillus enters the organ. Infection of the liver by the tubercle bacillus gives rise to miliary tubercles, or in the more chronic form, cheesy areas of various sizes, and, rarely, extensive caseation involving a large part of the liver, constituting the so-called cold abscess. Miliary tubercles and miliary gummata are

FIG. 369.—SYPHILITIC CIRRHOSIS OF THE LIVER.—(*Schmaus.*) × 40 diameters.
a. Liver capsule. *b, b, b.* Newly formed connective tissue, which is grouped in a band-like area as at *g*. *c.* Branch of portal vein. *l, l, l.* Liver lobules. *e.* Deep fissure produced in the liver surface by the traction exerted by the fibrous bundles, *g.*

often quite similar, and a microscopic or bacteriologic examination may be necessary to differentiate the lesions. Miliary tuberculosis of the liver usually produces marked enlargement of the organ. It is frequently concurrent with peritoneal tuberculosis, which may be interpreted as indicating that the infection has arisen in the portal system or that the peritoneal lesion is secondary to the hepatic manifestation. In acute cases the tubercles are small and of the gray type (p. 149); after the lesion has persisted longer they become yellow and often distinctly caseous. Localized tuberculosis of the liver is manifested by caseous nodules called solitary tubercles. The term solitary must be given the same liberal construction as when applied to solitary abscesses; both

lesions are frequently multiple. The solitary tubercle is a circumscribed caseous area surrounded by a capsule which may be thick and dense or exceedingly thin. The tuberculous abscess usually results from secondary infection of a solitary caseous area. When the cheesy nodules rupture into a bile-duct, caseous cholangitis commonly follows.

Actinomycosis of the liver[1] may be primary or secondary; of Aribaud's seven cases of primary hepatic actinomycosis, Auvray believes that three are genuine. Of the thirty-one cases collected by Auvray, seven were due to direct extension from the alimentary tube; eleven were infections by the portal blood. Propagation from the kidney or lung is less frequent. Abscesses, miliary, multiple or single, always develop. The liver becomes adherent to the abdominal wall or some contiguous viscus, and extending necrosis gives rise to fistulous paths and external openings; all the reported cases have proved fatal. The diagnosis is made by demonstrating (p. 167) the fungus in the tissues or discharges.

Leprosy of the liver is a rare manifestation of the tubercular or nodular form of the disease, The histology of the leprous nodule is described on p. 159.

Tumors of the Liver.—Adenoma may arise from the liver cells or from the epithelium of the intrahepatic ducts. Birch-Hirschfeld observed adenoma of the liver twice in 400 autopsies on infants. Hypernephroma (see p. 662) of the liver has been described. The most important of the hepatic tumors are the carcinomata, which may be primary or secondary. Hale White, in 10,000 postmortems, found ten undoubted instances of primary cancer of the liver;[2] the secondary cancers were twenty-four times as frequent. Eggel collected 163 instances of primary hepatic cancer. It has been observed in children, but is rare before middle life. Primary cancer may arise from the hepatic cells or from the epithelium of the biliary ducts; it may be of the cylindric-cell type or resemble the glandular cancers. Nodular, massive or solid, and diffuse forms are recognized. The first of these consists of bossed, irregular nodes, usually grouped in one area of the liver, commonly the right lobe. Massive or solid tumors consist of a single growth. Less than one-fourth of the primary cancers are of this form. The diffuse form is the rarest of hepatic cancers; it gradually infiltrates a lobe, and on account of the large amount of connective tissue, contracts about as rapidly as it destroys the hepatic structure, thereby preventing any considerable increase in the size of the organ. The usual form of hepatic cancer is secondary to carcinoma in some part of the intra-abdominal alimentary canal. Some of these tumors attain enormous dimensions; in the case reported by Christian the liver weighed 15,110 gm. The secondary growths are practically always multiple, and usually are distributed in the liver from a portal vein. The multicentric character of the growth leads to the production of a large number of nodes, many of which are near the surface, upon which they may be recognized as slightly elevated bosses; as a result of degenerative and necrotic changes in the

[1] Auvray, "Rev. de Chir.," July, 1903, p. 1.

[2] Christian, "Med. and Surg. Reports of the Boston City Hospital," 1902, thirteenth series, p. 166. Scheel "Nord. Med. Arkiv.," Feb. 11, 1902. Wells "Amer. Jour. Med. Sci.," Sept., 1903, p. 403. Burt, "Post-Graduate," Nov., 1903, p. 991.

interior and consequent contraction the center of the boss is depressed (umbilicated).

Connective-tissue tumors of the liver are rare—angiomata are probably the most frequent, and are practically always of the cavernous type; they are rarely large, although Mantle reported an instance in which the tumor was 20 cm. by 30 cm. Angioma of the liver[1] is congenital, although other views as to its origin have been expressed. Myxomata and fibromata are rarely found in the liver. Primary sarcoma of the liver is even less frequent than primary cancer. It may consist of a single large mass, or from such a primary growth there may be multiple nodules disseminated through the organ. Histologically any type of cell may be present. Melanotic tumors of the liver are probably always secondary.

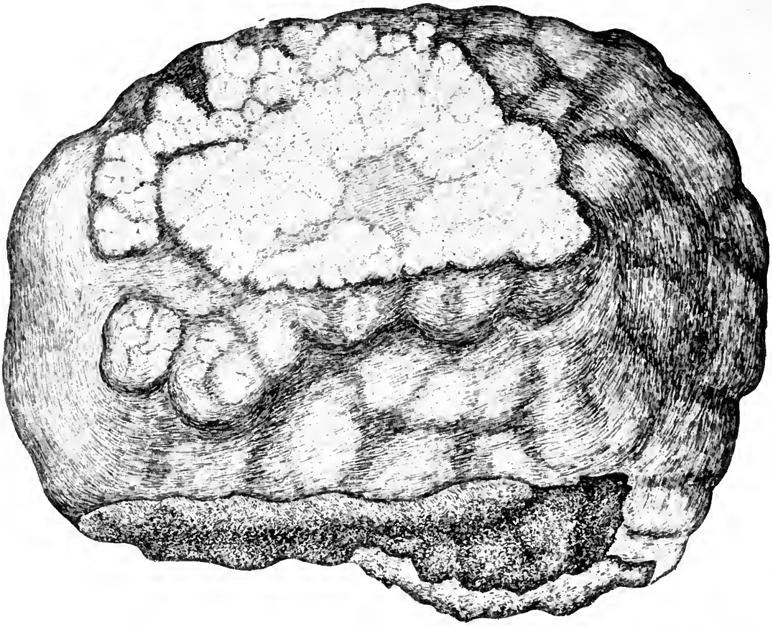


Fig. 370.—Part of Left Lobe of the Liver, Showing Primary Cylindric-cell Carcinoma. The slight umbilication of the cancerous nodules is indicated. Figure 174, page 328, is from a section of this tumor. (Removed by Professor Keen from a man fifty years of age. The illustration is three-fourths natural size. Mass weighed 525 gm. The patient recovered.)

Cysts of the Liver.—Some of the adenomata of the liver are cystic, and Boye[2] believes that the so-called cystic disease of the liver is really a form of cystadenoma. Cysts resulting from occlusion of the bile-ducts were considered when speaking of obstructive biliary cirrhosis (p. 756). Some, if not all, of the so-called simple cysts arise in this way. Those possessing a ciliated epithelial lining demand some other

[1] Schmieden, "Virchow's Arch.," 1900, Bd. clxi, p. 373. Ahaan, 'Ziegler's Beitr.," 1903, Bd. xxxiv, p. 215. Mantle, "Brit. Med Jour.," Feb. 14, 1903, p. 365.

[2] "Centralbl. f. inn. Med.," July 19, 1902.

explanation. A form of congenital cystic disease of the liver resembling that occurring in the kidney (p. 665) is occasionally observed. They are usually multiple, but a single large cyst is sometimes present. It is probable that they arise from developmental errors in the evolution of the bile-ducts. The most frequent cyst of the liver is the hydatid (p. 199), fifty per cent. of which are situated in the organ under consideration. Neisser, in 986 cases of hydatid disease, found the liver affected in 451. It is usually stated that hydatid cysts do not develop in the bile-ducts, but Dévé reports a case in which the cavities were lined by biliary epithelium. Figure 110, page 199, is a hydatid cyst of the liver; these cysts occasionally inspissate and may become caseous or cretaceous.

BILIARY PASSAGES.

Malformations.[1]—Occasionally the common duct, the duct of the gall-bladder, or the gall-bladder itself may be absent; in certain cases of jaundice in the new-born the ducts are either absent or not patulous.

Cholangitis, or **inflammation of the biliary ducts,** may be a catarrhal process, either *acute* or *chronic*, or it may be *suppurative*, and, in rare instances, *gangrenous*.

Acute catarrhal cholangitis is commonly secondary to duodenitis, but may also result from the presence of gall-stones or from hydatids, either in the liver or along the course of the biliary passages. The condition constitutes the anatomic basis of the so-called catarrhal jaundice, and is probably always of bacterial origin. It is generally maintained that infection is either ascending or descending; in the former the bacteria enter from the duodenum, and in the descending infections microorganisms are brought to the liver by the blood and excreted with the bile. The studies of Carmichael[2] indicate that the infection is practically always of the ascending type. Embolic abscesses within the liver and suppurating hydatid cysts may infect the bile-passages. Biliary ducts are frequently infected in typhoid and occasionally in pneumonia and other acute infectious diseases. Any obstructive lesion which impedes the flow of the bile favors infection and frequently gives rise to cholangitis. The inflammation of the ducts associated with cancer and other tumors involving the lower part of the biliary passages is primarily the result of obstruction and consequent infection. The changes in the mucosa are those seen in catarrhal inflammations of the mucous membranes. (See p. 546.) In the milder forms of the disease the patients rarely die, and therefore but little knowledge is available as to the changes occurring in the liver. When, however, the condition has persisted for any length of time, the liver is usually enlarged and the connective tissue surrounding the biliary passages shows more or less cellular infiltration. The lobules may contain areas of necrosis.

Chronic catarrhal cholangitis, or *chronic catarrhal inflammation of the bile-ducts*, arises as a result of the continued action of the causes already given when considering the acute form. The disease usually invades the gall-bladder; it may give rise to obstruction of the cystic duct, and thereby induce considerable dilatation.

[1] See Malformations of the Liver, p 739.
[2] "Jour. of Path. and Bact.," Sept., 1902, p. 276. Bibliography.

Suppurative cholangitis, also called **phlegmonous cholangitis,** is due to pyogenic infection of the biliary passages. The morbid process usually begins as, or is associated with, a catarrhal inflammation, and hence the causes already given for this process are to a certain extent influential in the production of the suppurative lesion. The disease may be secondary to cholelithiasis; it is not infrequently associated with general infections, such as occur in pyemia, pneumonia, typhoid fever, and influenza. The colon bacillus, the typhoid bacillus, and the usual pyogenic organisms are the bacteria most frequently present. As to the course of infection, it is probable that in most instances the bacteria reach the biliary passages from the intestinal canal by a process of direct invasion. It is not improbable that the infection may occur through bacteria carried to the hepatic tissues by way of the circulation, which, finding in the biliary passages conditions suitable for their growth, lodge and give rise to inflammation. Phlegmonous cholangitis may arise from, or terminate in, pyemia or septicemia. The suppurative process may be restricted to the gall-bladder (**phlegmonous cholecystitis**), in which condition the wall of the gall-bladder becomes edematous and infiltrated with leukocytes, which may accumulate in the interior in sufficient numbers to justify the conclusion that the contents of the gall-bladder is pus, constituting what is called **empyema of the gall-bladder.** Peritonitis may occur without perforation of the cystic wall, infection having traveled through the lymph-spaces. The gall-bladder is commonly greatly enlarged, and evidence of the septic character of the inflammation is further indicated by the systemic phenomena attributed to the absorption of toxic bodies from the area of infection. Whether the process began in the gall-bladder or originated in the common duct or its ramifications in the liver can not always be determined. When the biliary system is involved in a diffuse suppurative cholangitis, the liver is usually enlarged, and on section pus may be identified in and around the biliary passages, which not uncommonly show more or less dilatation. If the disease be permitted to progress, and if the patient survive, abscesses, macroscopically recognizable, may be found in the hepatic tissue. (See Hepatic Abscess, p. 749.)

Pseudomembranous or **fibrinous cholecystitis** is exceedingly rare; Rolleston[1] has reported a case.

Tuberculosis of the gall-bladder[2] or *tuberculous cholecystitis* is infrequent; it may involve the mucosa or interstitial tissue. It is usually secondary.

Pericholecystitis, or inflammation around the gall-bladder, may be of any type of serous membrane inflammation. Similar inflammatory conditions surrounding the biliary ducts are called **pericholangitis;** both are usually due to extension of inflammatory processes from the interior. In the chronic productive or fibrous form of pericholecystitis the gall-bladder is surrounded by masses of fibrous tissue, the wall greatly thickened, and the organ frequently adherent to contiguous structures. An interstitial cholecystitis has been described; it may be productive and associated with great thickening of the gall-

[1] "Trans. Path. Soc. of London," 1902, vol. liii, p. 405.
[2] Beitzke, "Centralbl. f. allg. Path. u. path. Anat.," Feb. 15, 1905.

bladder wall, or suppurative, in which case infection of the overlying peritoneum practically always occurs.

Obstruction of the biliary ducts, including the cystic duct, may be due to swelling of the mucosa, gall-stones, parasites, such as ascarides and flukes, and hydatid cysts; tumors within the ducts, neoplasms involving the contiguous glands, duodenum, or pancreas; adhesions and fibrous bands around the ducts, prolapsed kidney, hepatoptosis, and pseudomembrane within the passages may produce occlusion. A similar condition results from congenital atresia or absence of one or more of the ducts. Obstruction is commonly attended by dilatation of the passages above the lesion, and predisposes to infection and the various types of inflammation already described. **Hydrops cystidis felleæ** results from occlusion of the cystic duct; the gall-bladder is greatly dilated, and most of the biliary constituents, except cholesterin, are absorbed, leaving a colorless, viscid fluid resembling mucus; in some cases the contained liquid is thin and watery. Unless the condition has been preceded by inflammatory thickening, the wall of the gall-bladder is usually thin.

Cholelithiasis[1] includes the conditions which give rise to gall-stones and the changes that result from their presence in the biliary passages and gall-bladder. Biliary concretions, or **gall-stones,** usually consist of coloring-matter combined with calcium and its salts, particularly the carbonate and phosphate. Varying quantities of cholesterin are also present; in the transparent, almost colorless, or slightly yellow stones the largest percentage is found. Possibly other causes are not without influence, but the most important etiologic factor in the production of gall-stones is infection. Of 128 cases examined by Merck, in fifty-three per cent. the colon bacillus was present, either alone or with staphylococci or streptococci; the typhoid bacillus is often found, and may be demonstrable years after the primary infection. A number of observers have produced gall-stones by inoculating the gall-bladder. The frequency of cholelithiasis in different countries varies. In Strasburg 25.2 per cent. of all cadavers of persons over sixty years of age contain gall-stones; Bevan found that sixteen per cent. of the bodies in the Rush dissecting-rooms were affected. The size of the calculi varies from the so-called biliary sand to masses 12 cm. long and 5 cm. thick; as a rule, the larger the number, the smaller the size. Over 5000 have been observed in a single case. Their most common location is in the gall-bladder; they occur in the ducts in the following order of frequency: cystic duct; cystic and common ducts; common duct; cystic, common, and hepatic ducts; intrahepatic ducts. Beer doubts whether there are over 150 cases of intrahepatic cholelithiasis on record. Stones are often latent, and sometimes encysted or contained in pockets. Their dangers lie largely in the complications to which they give rise, the latter including all forms of inflammation of the gall-bladder and ducts, perforations, obstruction,

[1] The literature of this condition is extensive. The reader may consult the following articles, which will place him in touch with the earlier communications: Mayo, "Med. Record," Feb 21, 1903, p. 289. Ewald, "Amer. Med.," July 18, 1903, p. 95. Herter, "Med. News," Sept. 26, 1903, p. 586. Beer, "Med. News," July 30, 1904, p. 202. Bierring, "Jour. Amer Med. Assoc.," Oct. 15, 1904, p. 1099. Decker, "Münch. med. Woch.," li, No. 39.

and secondary degenerations and inflammations, within the liver, and intestinal obstruction. As a result of adhesions, the stone may be discharged by perforation into the stomach, colon, intestine, the pelvis of the kidney, or externally; in rare cases the diaphragm and the lung are penetrated.

Tumors of the Gall-bladder.—*Villous papilloma* of the gall-bladder occasionally occurs; it often terminates in *cancer*. The most frequent tumor of the gall-bladder is cancer; it is commonly secondary to gall-stones. The tumor is usually the cylindric-cell type of carcinoma. Primary connective-tissue tumors of the gall-bladder are exceedingly rare; fibroma, lipoma, and sarcoma have been observed.

Tumors of the Bile-ducts.—*Papillomata* and *cystadenomata* occasionally occur; they are most frequent in the vicinity of the ampulla. *Primary cancer* of the bile-ducts[1] is also most common in the same area. It also occurs at the junction of the common and cystic ducts, and is less frequent in the hepatic duct; it is usually the cylindric-cell type of cancer. In some cases the growth is primary in the ampulla of Vater. *Secondary carcinoma* of the bile-ducts is usually due to direct extension from duodenal, pancreatic, or gastric cancer, cancer of the liver, and secondary nodules in contiguous lymph-nodes; in rare cases cancer of the gall-bladder extends into the bile-ducts.

[1] Mayo, "Northwest. Medicine," April, 1903, p. 173.

CHAPTER XII.

PANCREAS.[1]

Normal Structure.—Histologically, this organ is a reproduction of the salivary glands, consisting of acini, with smaller ducts emptying into a larger duct (Wirsung's duct), the latter terminating in the duodenum in common with the hepatic duct. Recent investigations have shown that probably the most important structures in the histology of the organ are the islands of Langerhans, to the activity of which is generally attributed the production of an internal secretion. The islands are round or oval, and consist of convoluted blood-vessels and epithelial cells. They are equally abundant in the head and body of the organ, but are much more numerous in the splenic end.

Malformations[2] and malpositions of the pancreas are infrequent. There are nearly forty recorded instances of accessory pancreas; such bodies are found in the wall of the stomach (Plate XIX), duodenum, jejunum, or ileum, usually in the submucosa or extending through the muscular layer of the intestine. They consist of small nodules, rarely more than 2 cm. or 3 cm. in diameter; they may give rise to diverticula in the intestinal or gastric wall. The duct of Santorini may be absent or in rare cases is larger than the duct of Wirsung; accessory ducts are rarely encountered. Occasionally the normal ducts enter the intestine at unusual points. In the **pancreas divisum** the splenic end of the organ is joined to the head by a pedicle of fibrous tissue containing a duct and vessels. The **annular pancreas** more or less fully surrounds the duodenum. A bifid or lobulated pancreas is occasionally encountered. The tail of the pancreas may be pulled out of position by a misplaced spleen, to which reference has already been made. (See p. 431.) In Glénard's disease (visceroptosis or enteroptosis) there may be a slight downward displacement of the organ, but it is not, however, marked. Tumors and cysts occupying the retroperitoneal tissues may push the pancreas forward. Cancers involving the posterior surface of the head of the organ may render it distinctly palpable.

Postmortem changes in the pancreas sometimes give rise to conditions that are easily misinterpreted. Chiari has suggested that the process may begin during the agonal period. The alterations may be uniform throughout the organ or restricted to smaller areas; the presence of altered blood may be taken as an evidence of antemortem origin.

[1] The literature on diseases of the pancreas is quite extensive; the following recent additions to our knowledge contain references to the most important articles: Opie, "Disease of the Pancreas, Its Cause and Nature," 1903. Robson, "Lancet," 1904, vol. i. Trevor, "Practitioner," April, 1904, p. 570. Hewlett, "Jour. of Med. Research," May, 1904, p. 377. Sauerbeck, Ssobolew, Gutmann, Adler, "Virchow's Arch.," 1904, Bd. clxxvii, Supp. Heft. Karakascheff, "Deut. Arch. f. klin. Med.," 1904, lxxxii, pp. 60–89, also "Centralbl. f. allg. Path.," Dec. 31, 1904, p. 992. Hemmeter, "Amer. Med.," March 11, 1905, p. 393.

[2] Ruediger, "Jour. Amer. Med. Assoc.," April 18, 1903; bibliography.

The affected structures are soft, cloudy, and sometimes appear to contain more fluid than contiguous uninvolved areas. When gastric ulcer or cancer penetrates the pancreas, postmortem digestion is often extreme. Gas cysts in the pancreas due to the Bacillus aërogenes capsulatus or other gas-producing organisms are occasionally observed.

Hyperemia of the pancreas is normal during digestion and occurs in the initial stage of the acute inflammatory processes that affect the organ.

Congestion of the pancreas may be a part of a general abdominal congestion, and is most marked in the presence of a long-continued obstructive lesion within the heart, or may result from cirrhosis of the liver.

Hemorrhage into the pancreas (*pancreatic apoplexy* or *pancreatic hemorrhage*) is a recognized morbid process, although there is considerable doubt as to its occurrence independent of inflammation. Little is known of the cause of the condition; it may occur at any age, but is most frequent in middle life and later. It is occasionally associated with evidence of congestion, to which it has been attributed. Bunge has suggested that it may be of embolic origin, and others have thought that arteriosclerosis is a cause. It is alleged that the continued use of alcohol favors its occurrence. It is probable, however, that the alcohol is only indirectly responsible for the process, causing a catarrhal duodenitis, which, in turn, is followed by pancreatic apoplexy. Inherited syphilis and infectious processes in the new-born are not infrequently associated with pancreatic hemorrhage. Exactly what the connection is can not, however, at present be definitely stated. The most important cause is cholelithiasis, especially when a gall-stone occludes the opening of the ampulla into the intestine and permits retrojection of bile into the duct of Wirsung. Crushes and blows on the abdomen may give rise to hemorrhage in and around the pancreas.

Morbid Anatomy.—The hemorrhage may be slight, consisting of punctate extravasations scattered through the organ; the extravasations may be restricted to the interstitial tissue, or the blood may enter the gland acini. In other cases the hemorrhagic infiltration is uniform throughout a part of the gland, commonly the head; and in still other instances the whole gland is affected. Occasionally, the hemorrhage involves the tissues around the organ, extending to the mesentery and retroperitoneal wall. The density of the organ is partly dependent upon the age of the hemorrhage, its extent, and the condition of the tissues before the hemorrhage took place. The suffused tissues are sometimes soft, as a result of liquefactive changes, or dense in consequence of coagulation. The hemorrhages may have occurred at different times, as shown by the fact that in some areas old pigment is found adjacent to, or in the vicinity of, manifestly recent extravasations. The source of the hemorrhage can seldom be located. Even in the mild cases without extensive infiltration of the organ, recovery unassociated with inflammation rarely if ever occurs. In the majority of cases, however, the lesion terminates in an acute inflammatory process. (See Acute Hemorrhagic Pancreatitis, below.)

Fatty infiltration of the pancreas is uncommon; it is sometimes a part of general obesity, results from retardation of the intra-abdominal circulation, or is secondary to atrophic degenerative and fibroid processes

occurring in the organ. *Calcareous infiltration* may accompany fat deposits or may follow hemorrhage or inflammation of the organ. The calcific material is occasionally diffuse and scanty in amount, or it may be collected in masses in some part of the organ. It is often difficult to decide whether the cretaceous matter lies within the ducts and is a manifestation of pancreatic lithiasis or has resulted from calcific changes in the necrotic areas.

Cloudy swelling, according to Ghedini,[1] occurs particularly in the acute infectious diseases, pyemia, and septicemia. I have seen it in typhoid, pneumonia, and erysipelas, and the condition is especially marked in protracted infections with high temperatures. Ghedini has observed **fatty degeneration** of the pancreas in chronic tuberculosis, cirrhosis of the liver, and in cardiac and pulmonary affections characterized by venous stasis. Opie and others have described **hyaline transformation** of the bodies of Langerhans; this change is most frequent in chronic inflammatory conditions in which the new connective tissue penetrates the lobules.

Atrophy of the pancreas, in the large majority of cases, is secondary to fibrosis involving the connective tissue of the organ, and constituting what is commonly described as chronic pancreatitis, which will be discussed with inflammations of the pancreas. After middle life the pancreas not infrequently participates in the atrophic changes involving many of the glandular viscera, muscles, and other organs.

Pancreatitis (*inflammation of the pancreas*) may be *acute* or *chronic*. The acute form is usually subdivided into the *acute hemorrhagic* and *acute suppurative;* a *gangrenous* type is also recognized.

Acute hemorrhagic pancreatitis results from the same causes as pancreatic apoplexy referred to above. Germain and Christian[2] have reported a case in which inflammatory phenomena without hemorrhage were present. Opie believes that pancreatic hemorrhage and hemorrhagic pancreatitis can not be separated. All are agreed that acute pancreatitis is essentially hemorrhagic. Many are convinced that the hemorrhage never arises independently of inflammation, and if the embolic and traumatic cases, and occasional instances of arteriosclerotic hemorrhage, are excluded, I am willing to subscribe to the prevailing opinion. Macroscopically, acute hemorrhagic pancreatitis, prior to the occurrence of hemorrhage, possesses no distinctive character by which it can be differentiated from digestive changes occurring in the organ. In the case studied by Germain and Christian the pancreas appeared normal. Hemorrhage rapidly ensues, and the picture is then identical with that of pancreatic apoplexy described above. In addition to the enlargement of the pancreas and the diffuse or circumscribed infiltration by blood there occur in the organ, in the peripancreatic fat, and in the fat of the mesentery, omentum, and abdominal wall, areas of fat-necrosis such as are described on page 253. The extent and size of the necrotic lesions vary; in the mild cases there are but few points of necrosis, in other instances large areas are involved. The serum of the general peritoneum is usually blood-tinged, and in the cavity of the lesser omentum the blood staining is usually marked. If the patient survive, the area of necrosis be small, and the escape of pancreatic secretion be arrested,

[1] "Rif. Med.," Aug. 23, 1904.
[2] "Jour. Amer. Med. Assoc.," Sept. 24, 1904, p. 888.

ultimate recovery sometimes occurs. In more marked cases, when the patient lives long enough, the pancreas softens, and becomes dark red, purplish, and eventually slate colored or black. In the later stage infection is almost invariably present, inducing a fetid odor; the pancreas has become gangrenous, and the lesion is now called **gangrenous pancreatitis.** The extent of the pancreatic and contiguous necrosis is determined by the size of the area originally involved. The dead tissue may lie in an abscess cavity formed by the lesser omentum, or in rare instances the suppurative and necrotic process penetrates the intestine

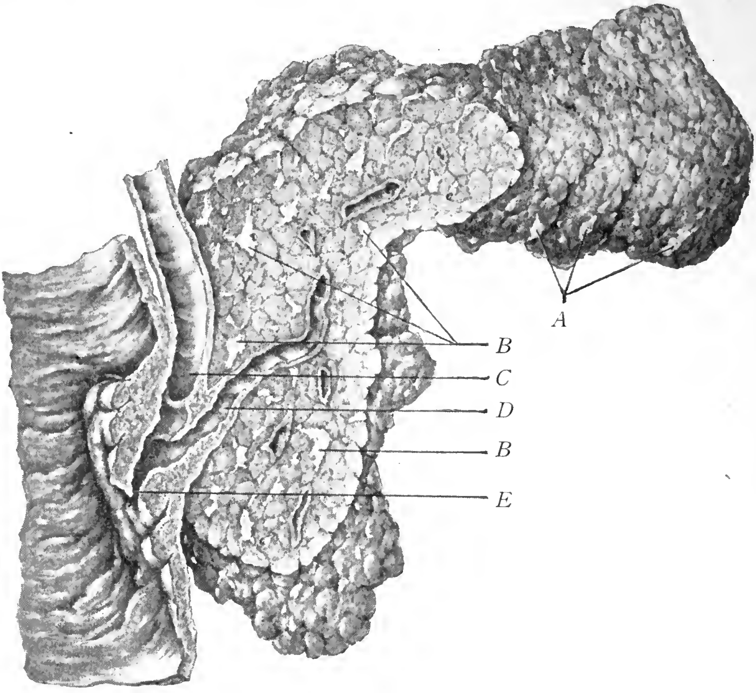


FIG. 371.—ACUTE PANCREATITIS WITH FAT-NECROSIS (Douglas).
This section of the pancreas, duct of Wirsung, and bile-duct makes evident the ease with which the bile may enter the pancreatic duct when a stone becomes lodged in the papilla, below the junction of the common bile-duct and the duct of Wirsung. Retrojection of bile into the duct of the pancreas is a most important factor in the production of pancreatitis. *A*. Areas of fat-necrosis upon the surface of the pancreas. *B*. Areas of fat-necrosis within the parenchyma of the gland. *C*. Ductus communis choledochus. *D*. Ductus pancreaticus. *E*. Papilla of Vater, opening of the ducts into the duodenum by a common aperture after junction just above

into which it empties. Acute inflammation of the pancreas is frequently associated with, and is usually due to, cholelithiasis and inflammatory conditions affecting the bile-ducts. The splenic enlargement observed in some cases may have arisen independently of the pancreatic lesions or was the result of sepsis. Thrombosis of the splenic vein sometimes follows the pancreatic lesion and is of septic origin.

Acute suppurative pancreatitis assumes a number of forms, depending upon the source of infection and the presence or absence of previous disease of the organ. It may be a part of a general sepsis, in which

case the multiple abscesses scattered through the organ are, of course due to the deposit of infected emboli. In other cases the suppurative process is restricted to the pancreas, and may be secondary to, or really a part of, the acute hemorrhagic or gangrenous pancreatitis already described. The lesion may be multiple; a single massive abscess or one of considerable size may result from confluence of many smaller abscesses. In the suppurative pancreatitis not preceded by the hemorrhagic lesion, fat necrosis is inconspicuous or absent. The abscesses may penetrate the abdominal cavity, giving rise to general septic peritonitis; or they may be evacuated through the stomach or intes-

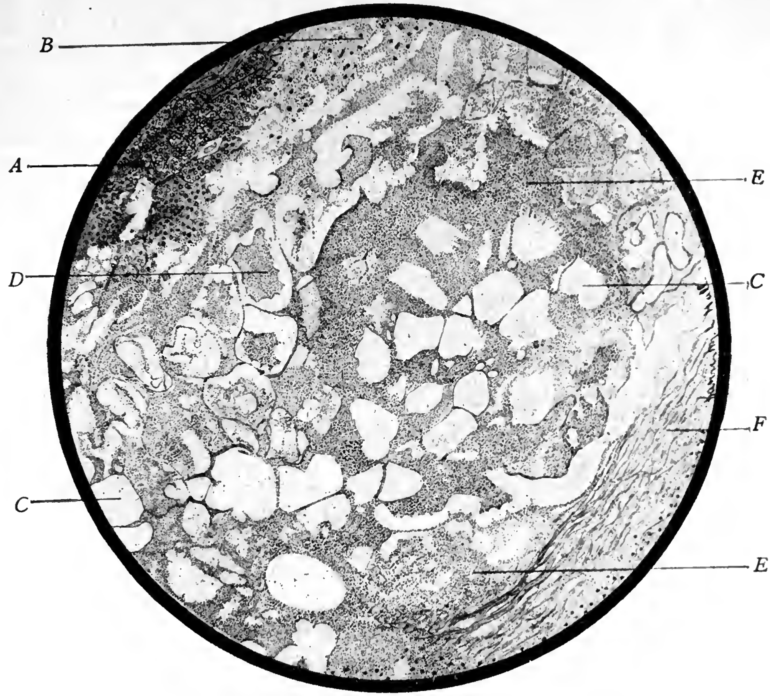


FIG. 372.—FAT-NECROSIS ACCOMPANYING ACUTE HEMORRHAGIC PANCREATITIS.

The area shown in the illustration is from just beneath the investing fibrous tissue of the pancreas. (For description of process see page 253.) *A*. Margin of area of hemorrhage. *B*. Fragmented nuclei in area of necrosis. *C, C*. Fat-cells that have escaped destruction. Many other unaffected or but slightly changed fat-cells are present. *D*. Fat-cell in which the necrosis is not complete. *E, E*. Areas in which the necrosis is practically complete *F*. Part of peripancreatic fibrous tissue.

tine; it is possible that a small purulent collection may inspissate. The author has seen what he believes to have been such a condition. The suppurative process may be more or less chronic in point of time, and sometimes induces a varying amount of fibroid change in the gland structure.

Chronic pancreatitis, *pancreatic sclerosis*, *indurative pancreatitis*, and *pancreatic fibrosis* are names given to a chronic process involving the pancreas and associated with the formation of a noteworthy amount of fibrous tissue.

Causes.—The lesion may be congenital or may be seen so soon after birth as to lead to the belief that it must have been in progress during intra-uterine life. Such fibroid changes are probably secondary to congenital syphilis. The cause of the lesion in adult and middle life, after which time it becomes more conspicuous, is probably duodenal catarrh and subacute or chronic catarrhal inflammation of the pancreatic ducts. The changes observed by Hoppe-Seyler[1] in the arteriosclerotic pancreas properly belong with this group.

Morbid Anatomy.—The amount of fibrous tissue may be such as distinctly to increase the size of the organ. In most cases, however, there is contraction, with atrophy of the glandular structures, and induration of the entire organ, or only a part of the pancreas may be involved. The tissue resists incision, and may be sufficiently fibroid to creak under the knife. Occasionally it is calcareous. The duct may be normal or dilated. The pancreas is sometimes reduced to one-fourth or one-fifth of its normal weight. Histologic examination of the organ, when chronic interstitial inflammation is present, discloses a notable increase in the interstitial tissue. In some cases it may be possible to surmise the origin of the condition by the location of the added fibrous tissue. When the irritation giving rise to the fibrosis has resulted from obstructive lesions in the ducts, the sclerosis is most marked around these structures. In the older areas the fibrous tissue is dense; when the lesion is progressing, the new tissue is cellular, containing lymphoid and plasma cells and sometimes eosinophiles. Opie distinguishes a **chronic interlobular pancreatitis** in which the new tissue is most conspicuous between and around the lobule, not affecting the islands of Langerhans; at most these structures are involved late, often after the acini are almost entirely destroyed. The second form described by Opie, he calls **chronic interacinar pancreatitis.** In this type the sclerosis around the lobules is less marked, the fibrosis contiguous to the islands of Langerhans is intense, and within the latter structures con-

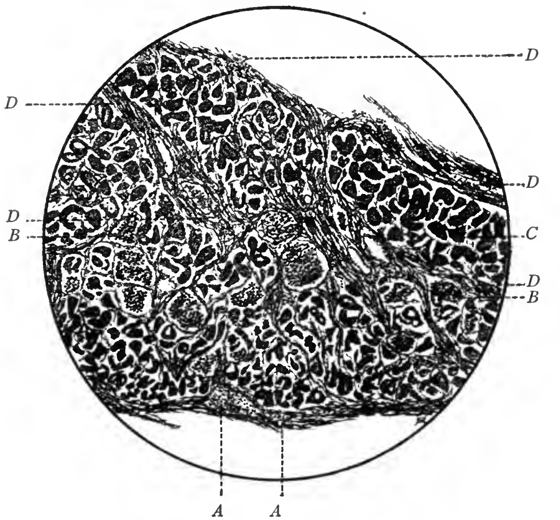


FIG. 373.—PANCREAS SHOWING INCREASE OF FIBROUS TISSUE. CHRONIC INTERSTITIAL PANCREATITIS.

A, *A*. Areas of hemorrhage. *B*, *B*. Immature gland cells (bodies of Langerhans). *C*. Gland acinus. *D*, *D*, *D*, *D*, *D*. Fibrous tissue; the areas of rhexis (*A*, *A*) are also in the fibrous tissue. (From a case of congenital syphilis.)

[1] "Deut. Arch. f. klin. Med.," Bd. lxxxi, p. 119.

PLATE XXI.

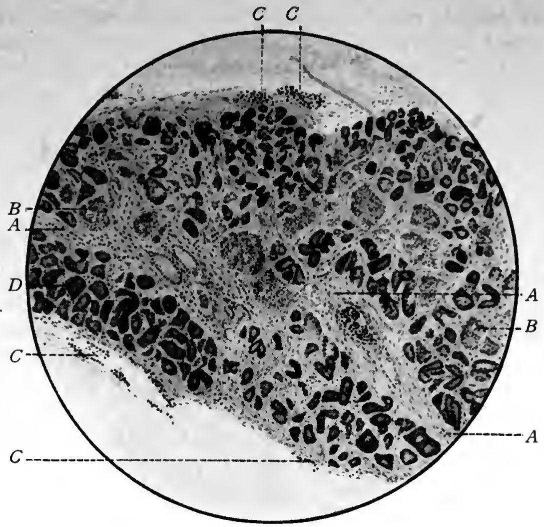


FIG. 1.

PANCREAS, CHRONIC INTERSTITIAL PANCREATITIS.

Evidently just prior to death, possibly in the agonal stage, multiple hemorrhages formed.

A A A. Notably increased fibrous trabeculæ. *B B*. Two of the numerous bodies of Langerhans shown in the field. *C C C*. Areas of microscopic hemorrhage. *D*. Nearly normal acinus; near center of field the acini are undergoing atrophy.

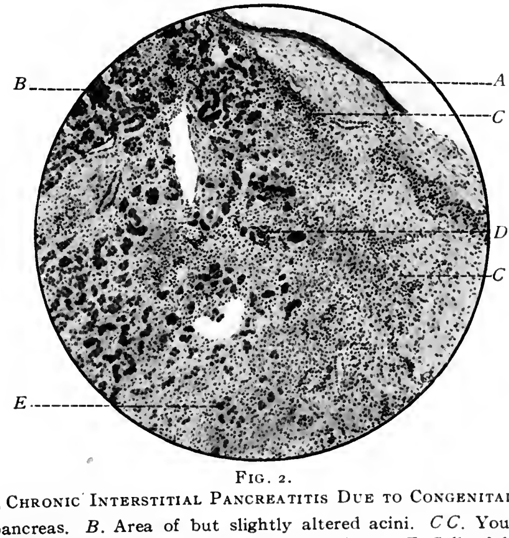


FIG. 2.

PANCREAS, CHRONIC INTERSTITIAL PANCREATITIS DUE TO CONGENITAL SYPHILIS.

A. Capsule of pancreas. *B*. Area of but slightly altered acini. *C C*. Young fibroblasts in the midst of areas of fibrous tissue production. *D*. Small hemorrhage. *E*. Cells of disappearing acini.

nective-tissue proliferation also occurs. Pearce[1] has shown that the islands of Langerhans are unaffected by the advanced interstitial change occurring in the chronic pancreatitis due to congenital syphilis.

Pancreatic calculi[2] are produced by causes similar to those operative in the formation of gall-stones. As the pancreas possesses two ducts, obstruction and consequent stone formation are less frequent. The calculi are oval or elongated, and sometimes branched, like coral. In the case reported by Schupmann the concretion was 6 cm. long and 1 cm. thick; 300 have been observed in one case. They are composed of cellular detritus, phosphate, and also carbonate of lime, and often contain bacteria. In seventy-two cases of diabetes studied by Hansemann pancreatic calculi were present in twelve. They may give rise to abscess formation and sinuses and be discharged externally. The associated obstruction and inflammation of the duct often induce a chronic interstitial pancreatitis.

Syphilis of the pancreas[3] is not a common affection. The chronic pancreatitis of hereditary syphilis I have described above. Accompanying that form of lues gummata are occasionally observed. Syphilitic endarteritis may produce sclerosis in the adult pancreas. Tertiary syphilis is sometimes manifested by the presence of syphilomata, which may obstruct the pancreatic duct or bile-duct; Trinkler suggests that this is the cause of jaundice occasionally seen in syphilis.

Tuberculosis of the pancreas is infrequent and probably is never primary. In disseminated miliary tuberculosis the pancreas is not always affected, and even when tubercles are present, they are rarely abundant. Caseous areas are sometimes found, and extending tuberculosis of contiguous lymph-nodes may penetrate the organ.

Tumors of the pancreas[4] are uncommon; in 13,000 autopsies there were 133 cancers, 2 sarcomata, 1 adenoma, 2 cysts, and 1 syphiloma. The most important of these tumors are the carcinomata, which may be primary or secondary. It is probable that most of the primary cancers begin in the head of the organ, although at autopsy practically all of the pancreas is often involved. In many of the cases it is impossible to determine the exact origin[5] of the neoplasm; the definitely cylindric-cell epitheliomata probably arise from the ducts; the glandular cancers are presumably from the epithelium of the acini. Carcinomata of the scirrhous type are probably the most frequent. Secondary carcinomata of the pancreas result from extension of primary growths situated in the stomach, duodenum, the ampulla, or biliary ducts. Metastases by the blood and lymph streams are less common. The occurrence of diabetes in pancreatic cancer is attributed to neoplastic destruction of the islands of Langerhans.[6]

Cysts of the pancreas[7] are divided into those arising within the gland

[1] "Amer. Med.," Dec. 26, 1903, also "Albany Med. Annals," Jan., 1904, p. 88.

[2] Moynihan, "Lancet," Aug. 9, 1902, p. 355. See also Pende, "Policlinico," 1905, p. 112, and "La Presse Méd.," April 8, 1905, p. 224.

[3] Trinkler, "Deut. Zeit. f. Chir.," Bd. lxxv.

[4] Nicholls, "Jour. of Med. Research," 1902, vol. viii, No. 2, p. 385.

[5] Falozzi, "Ziegler's Beitr.," Bd. xxxiv, H. 2, p. 199.

[6] Pearce, "Amer. Jour. of Med. Sci.," Sept., 1904, p. 478.

[7] Park, "Amer. Med.," June 13, 1903, p. 949. Lazarus, "Zeit. f. klin. Med.," 1904, vol. li. Gouraud, "Gaz. des Hôp. Civils et Militaires," April 2, 1904. Robson, "Lancet," April 2 1904, p. 911.

—true pancreatic cysts—and cysts situated in the neighborhood of the pancreas—pseudopancreatic cysts. The first of these include the retention cyst,—pancreatic ranula,—congenital cystic disease of the pancreas, cystadenoma of the pancreas, and hydatid cysts involving the organ. **Pancreatic ranula** may develop as a monolocular cyst, near the duodenum, or a series of dilatations distributed along the duct of Wirsung. If the pancreas possess its normal number of ducts, a retention cyst is rarely formed. Small cysts occupying the lobules of the organ—**acne pancreatica**—result from obstruction of the smaller ducts. **Congenital cystic disease of the pancreas** is a rare affection, often associated with similar formations in the kidneys and liver. The cause of the condition is unknown; the cysts are usually multilocular, and the entire organ may be involved. **Cystadenomata** (p. 368) are definite neoplasms of the pancreas and are rare; the cavities may contain papillary masses and but little fluid. **Pseudopancreatic cysts** result from liquefaction necrosis, hemorrhage in noninflammatory exudates situated in the peripancreatic tissues, and include fluid accumulations in the lesser peritoneal cavity. Some of the pseudocysts communicate with the pancreas, and probably a few of them are the direct consequence of pancreatic disease. They are frequently the result of injury, and when due to this cause, are called **traumatic pancreatic cysts.** The contained fluid is highly albuminous and often bloody. Cysts arising from or communicating with the pancreas usually contain one or more of the digestive ferments manufactured by the organ. In the case reported by Phillips the fluid was clear and possessed a specific gravity of 1.002, which is exceptionally low. It is usually brown or chocolate colored, sometimes contains clots of blood, and is nearly always alkaline in reaction.

CHAPTER XIII.

DUCTLESS GLANDS.

THYROID GLAND.[1]

Normal Histology.[2]—The thyroid gland as found in the adult is composed of vesicles or follicles, round or oval, measuring from 35 μ to 125 μ in diameter. The epithelial wall of the follicle is formed by a single layer of columnar epithelium. These cells vary in height, and are placed directly upon a slightly condensed connective-tissue layer, which does not possess the usual characters of a basement membrane. The follicles contain a homogeneous colloid body, which gives slightly different reactions even in adjacent follicles, constituting two forms of the substance, known as clear and dark colloid. There is an unusually rich supply of blood-vessels and lymphatics in the surrounding connective tissue. Sometimes lying within the thyroid, and at other times some distance away, are bodies resembling embryonic thyroid tissue, and composed of epithelium arranged in columns, but not forming distinct follicles, sacs, or tubes, and containing no characteristic colloid substance. That these bodies are not simply accessory, immature, or imperfectly formed thyroid elements is indicated by the fact that their development is completed before that of the thyroid gland. Experimental evidence goes to show that they may, however, assume some of the characters of the normal gland, and possibly part of its function, especially when the latter has been removed or destroyed. These bodies are known as **parathyroids.** The number of parathyroids varies, rarely, however, exceeding four. The fact that the removal of the thyroid gland induces changes resembling those seen after the removal of the parathyroids would further indicate that the function of the latter is accessory or compensatory to the former, and in man, as well as in lower animals, the removal of the thyroid may not be followed by symptoms, the parathyroids assuming the functions of the removed gland.

Malposition and Malformation of the Thyroid.—The gland may be absent; only one lobe is sometimes present. The isthmus is frequently abnormal; it occasionally consists of a narrow band of fibrous tissue in which there is no thyroid structure. In other instances it forms the base of a pyramidal lobe extending upward along the anterior surface of the trachea, following the course of the normally obsolescent duct; along the course of the latter structure irregular masses of thy-

[1] For recent exhaustive study of pathology of the thyroid see Dudgeon, "Trans. of Path. Soc. of London," vol. lv, p. 151. Also Edmunds, "Lancet," 1901, vol. i. For recent clinical treatise consult Richardson, "The Thyroid and Parathyroids," 1904.

[2] For recent studies see Flint, "Amer. Jour. of Anat.," Dec., 1904, p. 77. For recent review of physiology of the thyroid and parathyroids see Vincent and Jolly, "Jour. of Physiol.," 1904, xxxiii, p. 65; also Kishi, "Virchow's Arch.," 1904, Bd. 176, p. 260.

roid tissue are sometimes present. Aberrant masses of thyroid tissue are occasionally observed; they may be along the track of the thyroglossal duct, in the tracheal submucosa (p. 575), in the submaxillary region, on the floor of the mouth, in the mediastinum, and at almost any point in the neck. The aberrant thyroid tissue may represent the entire gland, and hence should not be removed until the surgeon has assured himself that other thyroid tissue is present.[1] Such misplaced thyroids may give rise to ectopic goiter—lingual goiter, tracheal goiter,[2] submaxillary goiter, and mediastinal goiter. The thyroglossal duct may persist[3] and, if patulous, constitutes a **thyroglossal fistula;** when closed at both ends, a cavity containing modified thyroid secretion, and

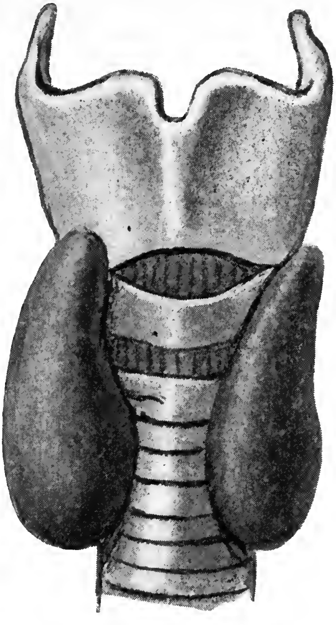


FIG. 374.—THYROID GLAND, ABSENCE OF ISTHMUS.—(*Marshall, courtesy of Dr Richardson.*)

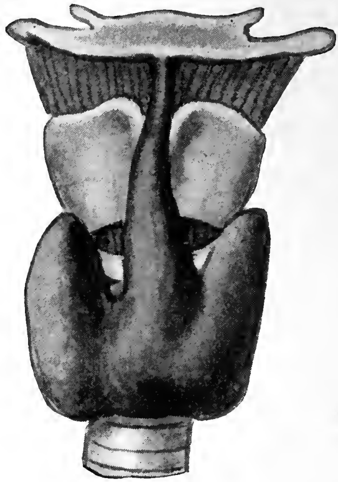


FIG. 375.—THYROID GLAND LARGE PYRAMID, SO CALLED PYRAMIDAL LOBE.—(*Marshall, courtesy of Dr. Richardson.*)

called a **thyroglossal cyst,** occasionally develops. Abnormally placed goiters, which undergo carcinomatous transformation, are known as **ectopic thyroid cancers.** Absence, atrophy or ectopia of the thyroid is occasionally accompanied by enlargement of the parathyroid.

Anemia, Hyperemia, and Congestion of the Thyroid.—Of a purely

[1] See discussion by Paton and also Spencer, Clin. Soc. of London. Feb. 10 1905; "Brit. Med. Jour.," Feb. 18, 1905, p. 357.

[2] Ferguson, "N. Y. Med. Jour.," Aug. 13, 1904, p. 289.

[3] Riesman, "Amer. Med.," June 29, 1901. Cornil and Schwartz, "Revue de Chir.," Dec. 10, 1904, p. 717.

local anemia involving the thyroid but little is known. Hyperemia is present in acute inflammatory processes, aside from which we have also an unusual vascular congestion, partly hyperemic and partly congestive, constituting the so-called vascular goiter. Congestion of the thyroid may be a part of the general venous distention occurring in cardiac diseases with failing circulation. There is also evidence of its presence, as previously indicated, in vascular goiter.

Atrophy of the thyroid undoubtedly occurs, but the exact factors influential in establishing this condition are but poorly understood. It is not improbable that inflammatory and productive processes induce a sclerosis analogous to that seen in other secreting organs with which we are more familiar. In further support of this view is the

FIG. 376.—THYROID GLAND SHOWING DOUBLE PYRAMID.—(*Marshall, courtesy of Dr. Richardson.*)

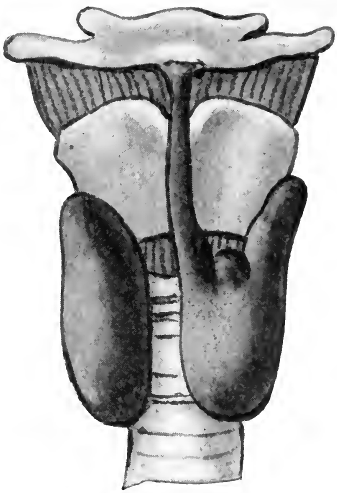


FIG. 377.—THYROID GLAND, ABSENCE OF ISTHMUS WITH PYRAMID ON LEFT SIDE. — (*Marshall, courtesy of Dr. Richardson.*)

well-known fact that occasionally cases of thyroid enlargement associated with exophthalmos, tremors, and rapid cardiac action (Graves's disease) show a progressive diminution in the size of the thyroid, which afterward remains small. The phenomena brought about by progressive atrophy of the organ usually are identical with those seen after the removal of the thyroid gland, the results of which have been studied in man, monkeys, and other animals.

The phenomena occurring in the patient are somewhat different when the thyroid gland has never been present—a condition constituting **sporadic cretinism,** or **congenital myxedema.**

The general disturbances of nutrition and arrest of development are usually not evident at birth, but commonly manifest themselves

within the first year. The stunted growth, which particularly involves the long bones, associated with thickening of the cranial bones, muscular weakness, intellectual deficiency, overgrowth of the subcutaneous tissue,—which may be myxedematous,—with yellowish, dry skin, brittle, scanty hair, protruding lips, thickened tongue, and more or less salivation, comprise the clinical and pathologic picture. Cretins rarely attain a height of five feet, and sometimes do not exceed three feet.

Closely resembling the condition just mentioned are the tissue and nutritive changes resulting from destructive processes attacking the thyroid gland. The destruction may be due to the occurrence of cysts, to fibrous deposits, or to tumor invasion, and constitutes a part of the anatomic basis of the disease called **myxedema.**[1] Myxedema usually occurs later in life; ninety per cent. of the cases are in women. The tissue changes resemble those seen in sporadic cretinism, except that the

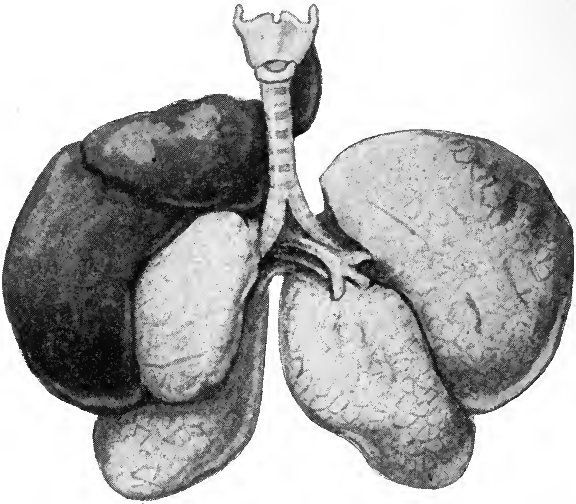


Fig. 378.—Intrathoracic Goiter Developed from Ectopic Thyroid.—(*Dittrich, courtesy of Dr. Richardson.*)

further development of the body, which may be completed, considerably alters the picture. There is a more conspicuous thickening of the subcutaneous tissues, with dry, rough, or scaly skin, broad and flattened digits, thick and overhanging lips, mental dullness, and evident poor nutrition of the hair, already mentioned as present in cretinism. The mucous membranes and submucous tissues show changes resembling those noted

[1] Millet, "Boston Med. and Surg. Jour.," Oct. 10, 1901. Abrikossoff, "Virchow's Arch.," Sept. 1, 1904, Bd. 177, p. 426. Russell, "Johns Hopkins Hosp. Bull.," June, 1904. Lanz, "Arch. f. klin. Chir.," vol. 74, No. 4. Thyroid aplasia and infantile myxedema see Pineles, "Wien klin. Woch.," Oct. 23, 1902, p. 1129. Changes in the central nervous system in cretins, see Bayon, "Neurolog. Centralbl.," April 16, 1904. For the relation of thyroid inadequacy to eclampsia, see Nicholson, "Brit. Med. Jour.," Oct. 11, 1902, p. 1138; also Sturmer, "Jour. of Obstet. of the British Empire," June, 1904. The occurrence of myxedema in alves, consult Seligmann, "Jour. of Path. and Bact.," March, 1904, p. 311.

in the skin. There is submucous tumefaction, particularly marked in the lips, mouth, and tongue, and sometimes in the palate. (See p. 247.) The teeth become carious, and sometimes fall out. It is well known that absence of the thyroid is commonly associated with mental hebetude, and consequently one would expect to find important histologic changes in the central nervous system; the structural alterations observed, however, are not always the same, nor are they constantly present. Bayon described hyaline changes in the vessels of the cortex without conspicuous abnormality in the ganglion cells; other observers mention vacuolization, pigment changes in the Nissl bodies (*tigrolysis*), and alterations in the chromatin (*chromatolysis*) of the ganglion cells; edema and occasionally hemorrhage may be present.

Cachexia Strumipriva (Postoperative Myxedema).—As a result of the clinical observations of Kocher, Reverdin, and others, and the experimental research of Horsley, Edmunds and Vassale, and Generali, it has been found that total ablation of the thyroid is followed by phenomena resembling those seen in cretinism and myxedema. The occurrence of this condition is dependent upon the more or less complete removal of the thyroid and parathyroids; the resulting disease is evidently due to the absence of thyroid function, as indicated by the fact that grafting of thyroids into thyroidectomized animals leads to the disappearance of the symptoms, and, further, that the administration of thyroid extract in this condition, as well as in cretinism and myxedema, arrests, or at least greatly modifies, the diseases in question. Apparently, these conditions are due to thyroid inactivity, insufficiency, or absence—and are correctly included under the term **athyroidism,** for which term *athyreosis*, *athyroidation*, and *athyroidea* are used synonymously.

Fig. 379.—Cretin Aged Twenty-two Years.—(*Wagner, courtesy of Dr. Richardson.*)

Hypertrophy of the thyroid will be considered with goiters and tumors of the gland.

Infiltrations and Degenerations.—Aside from the occasional presence of calcareous material in the thyroid gland, as well as hyaline substances and bodies resembling lardaceous material, nothing is known of the special forms of infiltration and degeneration occurring in this organ. Atrophied and fibroid thyroids frequently contain an excess of adipose tissue, the deposit of which appears to be distinctly secondary to the loss of gland-substance. Degenerative changes are constantly present in the epithelium lining the follicles; their significance, however, is not at present appreciated.

Of **thyroiditis, strumitis,**[1] or inflammation of the thyroid gland, but little is known; in various infections and toxic conditions an **acute nonsuppurative thyroiditis**[2] has been observed. The colloid is increased, proliferation and necrosis of the gland cells occur, the interstitial tissues are edematous and may contain a few leukocytes, of the mononuclear types, and hemorrhagic lesions are sometimes present. Roger and Garnier give 35 gm. as the normal weight of the thyroid; in the acute nonsuppurative inflammations the gland sometimes weighs 50 gm. to 55 gm. The condition is more frequent in infants than in adults, and has been studied particularly in variola. **Acute suppurative strumitis,**[3] also called *acute purulent strumitis*, may be diffuse or localized; the latter is called **thyroid abscess.** The causative bacteria may reach the gland from contiguous structures or by the blood; the latter form of the infection occurs in pyemia and usually gives rise to multiple abscesses. Thyroid suppuration occurring in the course, or as a sequel, of an infectious disease, especially typhoid, is due to hematogenous infection. In both the diffused and circumscribed suppurations the organ is enlarged, tender, and edematous. When the infection is diffuse, polymorphonuclear leukocytes are abundant in the interstitial tissue and may penetrate the acini in large numbers. A **chronic fibroid interstitial thyroiditis**[4] has been described; it may be diffuse in the interstitial tissue, or restricted to smaller areas (**insular thyroid sclerosis**). In some cases the gland acini are enlarged or even cystic; in other instances the vesicles are small and the epithelium wasted; the latter type corresponds to the diffuse sclerosis mentioned when discussing atrophy of the organ.

Tuberculosis of the thyroid[5] may be primary or secondary. The former is usually characterized by the presence of caseous or fibrocaseous areas in the gland, and is exceedingly rare. Secondary tuberculosis may result from extension of lesions primary in adjacent structures, especially the lymph-nodes, or hematogenous dissemination of the bacillus, particularly in miliary tuberculosis. The tubercle bacillus rarely colonizes in the thyroid gland; Lebert observed tuberculosis of this organ in 7 per cent. and Fränkel in 12 per cent. of the tuberculous cadavers examined.

Syphilis of the thyroid is exceedingly rare: the cause of the swelling sometimes seen in secondary syphilis remains undetermined. Gumma occasionally occurs. A nodular enlargement in congenital syphilis[6] has been described.

Goiter, struma, and *bronchocele* are terms applied to certain thyroid

[1] The term strumitis is often used for inflammation occurring in a goiter; the changes are essentially similar to those observed in the previously normal thyroid, and attempts to distinguish the two processes have been unproductive.

[2] Roger and Garnier, "La Presse Méd.," May 16, 1903, p. 373, and "Virchow's Arch.," 1903, Bd. 174, p. 14. Bayon, "Centralbl. f. allg. Path.," Sept. 30, 1904, p. 737. de Quervain, "Mittheilungen a. d. Grenzgebiet. de Med. u. Chir.," 1904, Bd. 13, H. 4 and 5, second supplementary band.

[3] Deleuil, "Thèse de Lyon," 1902. Abrajanoff "Chirurgia," Feb., 1903. Krause, "Berl. klin. Woch.," Aug. 17, 1903, p. 756.

[4] E. Perrin de le Touche and Marrice Dide, "Soc de Neurol.," Paris, Nov. 5, 1903; "Revue Neuro.," Nov. 30, 1903, p. 1120.

[5] Clairmont, "Wien. klin. Woch.," Nov. 27, 1902. Pupovac, "Wien. klin. Woch.," Sept. 3, 1903, p. 1012.

[6] Goulon, "Arch. de Méd. des Enfants," 1904, vii, p. 36.

enlargements of obscure origin. The condition is endemic in Switzerland, certain parts of France and Italy, and goitrous centers have been observed in the United States (Michigan, Pennsylvania). The affection has been attributed to causes arising in both water and soil, and also to atmospheric conditions. The recent studies of Grassi and Munaron[1] indicate that goiter is due to poisons elaborated by some organism inhabiting the soil and living outside of the human body. Several varieties of the affection are recognized. In **parenchymatous goiter** the affected tissue possesses a structure similar to that of the normal organ, although empty follicles and hyperplasia of the interstitial tissue are more abundant than in health. It is supposed that this form results from an increase in all the gland elements, and hence it is sometimes called **hyperplastic goiter.** In **colloid goiter** the cavities are larger, the walls thinner, and the increase in interstitial tissue less conspicuous. When the dilated gland spaces attain considerable size, the condition is sometimes called **cystic colloid goiter.** In this form the material contained within the cavities is unusually rich in colloid and in some cases mucin is present. Calcification of the wall occurs. The cysts are lined by epithelium which, in the earlier stages, is distinctly of the low columnar type, but later becomes flattened, granular, and occasionally fatty. **Fibroid goiter** is recognized by the large amount of fibrous tissue that it contains. The newly formed fibrous element may be uniformly disseminated throughout the mass, or grouped in islands irregularly distributed in the goiter; the latter type is sometimes called **nodular fibroid goiter.** In some forms of struma hemorrhages into the cysts, or interstitial tissue, occur, and in a way justify the name **hemorrhagic goiter.** In other cases the goitrous enlargement is composed of, or contains an enormous number of large vessels, usually veins, some

Fig. 380.—Unusually Large Cystic Goiter. (Redrawn from photograph.)

[1] "Rendiconti d. r. Accad. dei Lincei," Jan. 17, 1904, vol. xiii, p. 57.

of which formed a part of the normal gland and others are newly developed. This condition is called **vascular goiter,** or **telangiectatic goiter.** Goitrous enlargements of the thyroid gland may inflame, suppurate, undergo necrosis, or calcify; the process last named is the result of calcific deposit, usually in the stroma of the mass. **Neoplastic goiters** consist of definite tumors involving the thyroid; when the neoplasms are innocent, the enlargement is called **benign goiter.** The same term is also applied to the forms of thyroid enlargement, mentioned above, which are generally regarded as distinct from new growths. When sarcoma or carcinoma involves the gland, the condition is called **malignant goiter.**

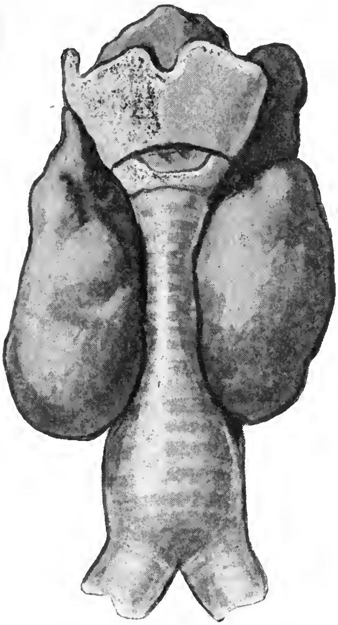


FIG. 381.—GOITER (BILATERAL) CAUSING COMPRESSION OF THE WINDPIPE PRODUCING THE SO-CALLED "BAYONET-SHAPED" TRACHEA.—(*Demme courtesy of Dr. Richardson.*)

A goiter may be unilateral or bilateral, or involve the isthmus. When arising from aberrant thyroid tissue, occupying an abnormal location, the term **aberrant** or **ectopic goiter** is sometimes used; as a rule, however, it receives its name from the position that it occupies—**lingual goiter, tracheal goiter, submaxillary goiter, mediastinal goiter.** With regard to the rapidity with which an enlargement develops it is possible to recognize **acute** and **chronic** goiters. In the simple goiters the symptoms produced are determined by the influence of the growth on contiguous tissues. The large vascular trunks and nerves of the neck may be pressed upon, or, what is more common, the trachea suffers. It may be flattened by bilateral or median growths, or, when the goiter is unilateral or one lobe is most affected, be displaced to one or the other side. The lumen is obstructed by an annular growth or bilateral pressure, pressure from in front or the development of a thyroid tumor in the submucosa (**intratracheal goiter**). **Lingual goiter** may obstruct the pharynx or encroach upon the laryngeal opening. **Mediastinal goiter** may press upon the lower trachea, bronchi, or other intrathoracic structures.

Exophthalmic goiter,[1] also called **Graves's disease,** or **Basedow's disease,** is an affection of unknown etiology, usually characterized by exophthalmos (prominence of the eyeballs), tachycardia, a peculiar form of muscular tremor, and enlargement of the thyroid gland; one or more of these so-called cardinal symptoms may be absent. It is clearly an intoxication—a toxemia; the character and origin of the poison are not definitely known, but the facts at our disposal indicate that it is

[1] Kocher, "Ueber Morbus Basedowi," 1902; 1423 references. Murray, "Lancet," Dec. 13, 1902, p. 1612. Salmon, "Clin. Med.," Aug. 3, 1904. Jellinck, "Wien. klin. Woch.," Oct. 27, 1904. MacCallum and Cornell, "Med. News," Oct. 15, 1904, p. 732.

some product, normal or abnormal, of the thyroid gland. When an excess of thyroid secretion is absorbed, symptoms resembling some features of Graves's disease may occur, and constitute what is called **hyperthyroidism** or **thyroidismus;** these phenomena may be experimentally produced, follow operations in which thyroid secretion escapes into the wound, or be due to other injuries of the gland. In Basedow's disease the blood content of the thyroid is increased, and hyperplasia of the epithelium of the acini is usually present, although there is no absolutely constant anatomic alteration in the gland. MacCallum and Cornell conclude that no adequate explanation has been given for the exophthalmos.

Tumors of the Thyroid.—**Adenomata** are occasionally observed; they are usually single and, as a rule, encapsulated; they are sometimes cystic with papillary growths in the interior (**papillary cystadenoma**). Low[1] has been able to collect ten such cases. **Cancer**[2] **of the thyroid** may be primary or secondary. The former is usually encephaloid and frequently grows rapidly, constituting the most fatal form of malignant goiter. Thyroid carcinoma is most frequent in goitrous glands; two-thirds of the patients are women. In the earlier stages the growth is within the capsule of the organ, but later it extends, involving the trachea and sometimes the esophagus. In over half the cases enlargement of the cervical lymph-nodes occurs. Secondary cancer involves the organ as a result of extension of a primary growth arising in the larynx, pharynx, trachea, branchial vestige, or other contiguous structure. **Fibromata, chondromata,** and **osteomata** are rare tumors of the thyroid. **Sarcoma** is an infrequent thyroid tumor occurring about one-fourth as often as cancer; of the fifty-three cases collated by Lartigau,[3] thirty-five occurred in goitrous glands. Round and spindle, or mixed cell sarcomata are the most common. In certain tumors of the thyroid it is impossible to decide whether the growth is a sarcoma or a carcinoma; these neoplasms have received the name **mixed tumors**[4] or **carcinosarcomata of the thyroid.**

FIG. 382.—EXOPHTHALMIC GOITER, BASEDOW'S DISEASE.—(*Courtesy of Dr. Richardson.*)

1 "Boston Med. and Surg. Jour.," Dec. 3, 1903.
2 Delore, "Rev. de Chir.," May 10, 1904, p. 680.
3 "Amer. Jour. of the Med. Sci.," Aug., 1901.
4 See Loeb, "Amer. Jour of Med. Sci.," Feb., 1903.

Dermoid cysts in the thyroid have been observed. Hydatids[1] of the organ occur, but are extremely rare; twenty-five cases are recorded.

Thyroid metastasis[2] is an extremely interesting condition characterized by the development of new growths composed of typical thyroid tissue in structures distant from the gland. In some instances the thyroid is not enlarged. The tumors are usually nonmalignant, and as a rule involve bones. In 7 of the 18 reported cases the cranium was affected; 14 of the patients were women.

ADRENALS.[3]

Malformation and Malposition.—The adrenal bodies may be absent or hyperplastic. Accessory bodies are occasionally observed. The supernumerary bodies may be near their normal position, or they may be in the capsule or cortex of the kidney, in or near the internal abdominal

FIG. 383.—SECTION OF CORTEX OF KIDNEY CONTAINING ECTOPIC ADRENAL. (Fixed in Heidenhain's solution paraffin, hematoxylin and Van Gieson Obj. 16 mm., oc. compensation, and reduced ⅓.)

A. Capsule of kidney extending over adrenal. *B, B, B*. Zona glomerulosa. *C, C*. Zona fasciculata. *D*. Zona reticularis. *E*. Capsule projected between adrenal and kidney cortex partly separating the two structures. *F*. Cavity surrounded by Bowman's capsule, external to which is adrenal tissue. *G*. Large vein. *H*. Kidney cortex. *I*. Imperfectly developed Malpighian body.

ring, inguinal canal, about the spermatic cord, in the epididymis or testicle, and in or near the ovary or broad ligament; they are also occasionally found in the liver. Ectopic adrenal cells constitute the histologic elements from which hypernephromata (p. 662) arise. Occasionally one or both the glands are hypoplastic.

[1] Rollet, Thèse de Lyon, 1902 and 1903, No. 163.

[2] Hollis, "Lancet," March 28, 1903, p. 884. Oderfeld and Steinhaus, "Centralbl. f. allg. Path.," 1903, vol. xiv, p. 84. Patel, "Rev. de Chir.," March 10, 1904, p. 398.

[3] For review of development, structure, and function of the suprarenal, see Minervini, "Jour. de l'Anatomie," Sept. and Oct., 1904. For recent study of the pathology of the suprarenal, see Karakascheff, "Ziegler's Beitr.," 1904, Bd. 36, p 401; also, Marchetti, "Virchow's Arch.," 1904, Bd. 177, H. 2, p. 227.

Atrophy of the adrenals is sometimes associated with fibroid change, may result from pressure, is not infrequently marked in old age, and occasionally is secondary to inflammatory processes occurring within the gland or in contiguous tissues. A simple atrophy has been described in which it is stated that the organs are no larger than peas. Medulla and cortex may be unequally involved.

Hypertrophy of the adrenals is rare; when one is absent or hypoplastic, or has been destroyed by disease, the remaining organ may enlarge. According to Marchetti, the hypertrophy is restricted to the cortex.

Infiltration of the Adrenals.—A gland otherwise normal may show a small amount of adventitious *pigmentation*, particularly in old age. As a rule, the pigment deposit does not involve the whole organ, but is restricted to one or more layers of the cortex, extending, to a certain degree, into the adjacent medulla. *Lardaceous disease* may affect the blood-vessels and, to a very limited extent, the connective tissue of the organ; the iodin and microchemic reactions (p. 230) are best seen in the cortex. *Calcareous infiltration* occurs in chronic infections that involve the gland, and is not infrequently present without any evidence of inflammation or tuberculosis.

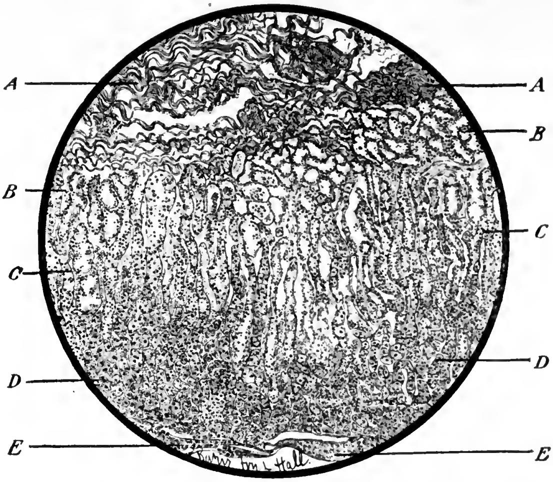


FIG. 384.—SECTION OF ECTOPIC ADRENAL BENEATH THE PERITONEUM AND INTIMATELY ATTACHED TO THE CAPSULE OF THE LIVER.
A, A. Capsule of Glisson. *B, B.* Zona glomerulosa. *C, C.* Zona fasciculata. *D, D.* Zona reticulata. *E, E.* Peritoneal surface.

Degeneration of the Adrenals.—*Parenchymatous* and *fatty degenerations* have been described, but little is known of their etiology or course. The former is frequently observed in infectious processes.

Hemorrhage into the adrenals,[1] or the adjacent fat, may result from trauma and is sometimes seen in intense congestion. It is particularly frequent in the new-born and in children. Toxic conditions, congenital syphilis, septicemia, pyemia, and gastro-intestinal infections proving fatal, are often associated with hemorrhagic infiltration of the adrenal. It is not known how these conditions induce the hemorrhage; it has been suggested that they act by altering the endothelium of the capillaries. The condition is also called **adrenal apoplexy** and is sometimes seen after severe burns, in which case it is apparently due to the accompanying toxemia. It may be diffuse or

[1] In addition to Marchetti and Karakascheff, see also Dudgeon, "Amer. Jour. of Med. Sci.," Jan., 1904, p. 134, and Langmead, "Lancet," May 28. 1904, p. 1496.

punctate, and sometimes forms a distinct hematoma. The later changes induced by the hemorrhage are not understood. It is possible that chronic fibroid induration or cyst formation is sometimes the result of interstitial hemorrhage.

Inflammation of the adrenal may assume an acute or a chronic type. Of the acute form but little is known, with the exception of an occasional suppurative lesion secondary to infection by means of the blood or involvement as a result of the extension of infection from adjacent suppurative processes. In the chronic form induration of the gland occurs, brought about by the production of new fibrous tissue; the lesion is, therefore, comparable to the chronic interstitial inflammations that involve other glandular viscera. Sergent[1] has described a chronic suprarenalitis of infectious origin and attended by the gradual evolution of adrenal insufficiency.

Syphilis of the adrenals may be manifested by the presence of gummata, which may be single or multiple; occasionally, a fibrosis of the organ occurs attributable to syphilis.

Tuberculosis of the adrenals is probably the most frequent disease to which the organs are liable. In general miliary tuberculosis the adrenal, in common with other organs of the body, is usually affected. The most frequent lesion of the adrenal, however, is the chronic fibrocaseous form of tuberculosis. The condition may be primary, but in a large percentage of cases is secondary. The tuberculous deposit usually begins in the medullary portion as scattered tubercles, which, by coalescing, convert the organ into a more or less caseous mass with a notable increase in the fibrous tissue or, not infrequently, extensive calcareous infiltration. The tuberculosis may extend from the gland proper to the surrounding tissues. Elsässer[2] found that in eighty-nine per cent. of the cases of adrenal tuberculosis both organs were affected.

Tumors of the Adrenals.[3]—The most frequent tumor connected with these organs is the hypernephroma described on page 662. It is usually stated that the most common neoplasm of the suprarenals is the *adenoma;* it is probable that some of these gland-like neoplasms have been confused with the hypernephroma. Adenomata are occasionally more or less diffuse, consisting of irregularly outlined nodules in the gland tissue; in other instances the tumor is sharply circumscribed, and sometimes encapsulated. Virchow described a form of adenoma that he termed *struma lipomatosa suprarenalis.* Such tumors simulate in structure the cortex of the organ. *Cancer* of the suprarenal may be primary or secondary. Adult connective-tissue neoplasms are extremely rare. *Sarcoma,* both primary and secondary, occurs, but is far less frequent than cancer. The *cysts* observed in the adrenals may result from hemorrhage into the gland substance or degenerative changes in adenomata. Hydatid cysts in the substance of the glands are occasionally observed.

Addison's Disease.[4]—Associated with tuberculosis, atrophy, simple

[1] "Arch. Gen. de Méd.," 1904, No. 1.

[2] "Arbeit. a. d. Path. Inst. Tübingen," 1904, Bd. 5, H. 1.

[3] See Woolley, "Amer. Jour. of Med. Sci.," Jan., 1903; bibliography.

[4] Vincelet, Thèse de Paris, 1902, No. 570. Wiesel, "Münch. med. Woch.," Oct 13, 1903. Simmonds, "Virchow's Arch.," 1903, Bd. 172, H. 3, p. 480. Abelous, "C. R. Soc. de Biol.," 1904, p. 952. Munch-Petersen, "Hospitalstidende," vol. xlvi, No. 50. Withington, "Med. News," Sept. 24, 1904, p. 591.

or inflammatory, neoplasms, or hemorrhage into the adrenals, there occurs a series of clinical phenomena to which has been applied the name Addison's disease. Although essentially a disease of adults Felderbaum and Fruchthander have collected twenty-five cases in patients under fourteen years of age. Tuberculosis of the suprarenal bodies is the lesion most frequently found (about 75 per cent. of the cases). Of the 216 cases collated by Vincelet, an associated pulmonary tuberculosis was present in 122; other organs were often involved. In addition to the change observed in the adrenal glands, a bronzing of the skin occurs, due to a deposit of pigment in the Malpighian layer. The cutaneous pigmentation is not uniformly distributed, but is usually most marked on the exposed parts. A similar coloration of the buccal mucosa may be present, and pigmented areas occur on the tongue. The nervous, muscular, and cardiovascular phenomena are not accounted for by the morbid anatomy. The disease is sometimes observed without demonstrable lesion of the suprarenal bodies. Of 281 cases examined by Lewin, twenty per cent. showed no lesion of these organs. It is usually held that the phenomena are caused by a suprarenal inadequacy. Abelous has shown that in twenty-four hours following the removal of the suprarenals of the frog the skin becomes much darker. The color is restored by injecting 0.1 mgm. to 0.2 mgm. of adrenalin into the lymph-sac; the restoration requires about eight hours for its full development.

CHAPTER XIV.

THE VOLUNTARY MUSCLES.

A **normal voluntary muscle** is formed of *fibers* held together by the *endomysium;* these, collected in larger groups, are surrounded by the *perimysium*, and in many localities the muscle is partly retained within a distinct sheath called the *epimysium*. The fibers forming the muscle vary in length, rarely exceeding, however, from 3 to 5 cm., and measuring from 10 μ to 50 μ in width. Each muscle-fiber is composed of a contractile substance with peripherally placed nuclei, and surrounded by a sheath called the *sarcolemma*. The various views with regard to the ultimate structure of the fibers will be found in works on histology and do not especially interest the pathologist.

Many **malformations** and slight alterations in the origin, course, and insertion of muscles occur. These, however, are of anatomic rather than of pathologic interest.

Atrophy of muscle[1] is observed under a number of conditions. Persistent pressure rapidly leads to disappearance of the contractile substance, with more or less substitution of fibrous tissue. A muscle not performing any function usually shows progressive wasting, constituting atrophy from disuse; such atrophies are intensified by associated pressure, as is seen when a fractured bone demands absolute rest and, at the same time, is subjected to the pressure of retentive dressings. Fixation of a joint (ankylosis), section of a tendon or muscle, and causes removing the force that induces normal muscular tension may also bring about atrophy. Interference with innervation, particularly the removal of motor stimulation as a result of diseases of the motor neurons or axons, may also bring about atrophy. Such atrophies are typified in the spinal and bulbar lesions of the central nervous system. As the disease usually begins in certain muscles, depending, of course, upon the location of the central lesion, and gradually progresses with the changes in the central nervous system, the term **progressive spinal amyotrophy** has been applied. (See Diseases of the Nervous System.) In the disease called *poliomyelitis*, particularly frequent in childhood, there occurs an acute inflammatory lesion involving the motor cells in the anterior horns of the spinal cord, with subsequent degenerative changes in these structures; as a result of the lesion in the cord, paralysis, followed by atrophic processes, involves the muscles controlled by the affected neurons, constituting a condition called *infantile paralysis*. (See Diseases of the Nervous System.) In other cases the atrophic process is unassociated with recognizable lesions of the central nervous system or peripheral nerve; in such instances the wasting is presumed to be essentially a disease of the muscle, and the term **primary myopathy** is applied. Certain of these atrophies closely resemble

[1] Babinski, "Soc Neurolog.," Dec. 1, 1904; "La Presse Méd.," Dec. 7, 1904, p. 784.

the progressive spinal form, and they have been grouped under the head of **progressive muscular dystrophy.**

Pseudohypertrophic muscular paralysis[1] (*myosclerosis*) is a disease most frequent in male children, although occasionally it is seen in girls; two or more members of the same family are frequently attacked. Usually, the first indications of the disease are observed in the muscles of the calves, which show considerable enlargement; this may be associated with corresponding increase in the volume of the anterior tibials. The marked enlargement commonly occurs in the gluteus maximus, and usually, although to a lesser degree, in the extensors of the thigh. The prominence of these muscles gives the appearance of hypertrophy, and hence the name. As the increase in size is associated with deficient contractile power (lessened function), the term pseudohypertrophy is appropriately applied. Associated with the increase in the size of the muscles indicated, others may show an early wasting—as, for example, the flexors of the knee and thigh. In the upper extremities the deltoid, supraspinatus, infraspinatus, and triceps are enlarged, while the biceps may be atrophied. Histologically, during the stage of enlargement the muscle-fibers occasionally show but slight alteration; there is, however, an enormous increase in the amount of fat between the fibers, to the presence of which the appearance of hypertrophy is due. (See Fig. 385, also Fig. 133, p. 227.) As a rule, the transverse measurement of the muscle-fiber is diminished, although occasionally fibers of unusual size are encountered. Later, there is a marked increase in the amount of fibrous tissue without corresponding continued overgrowth of the fat. The muscle-fibers become thin and irregular. The striation, at first nearly normal, rapidly grows less conspicuous, and eventually disappears. Fat has been observed within the sarcolemma, which, associated with the granular changes in the fibers, would indicate that the process is essentially a degeneration. The alterations in the contractile substance are not uniform and do not implicate at one time all the fibers in a given muscle, nor are all the fibers in one area simultaneously involved; it is, therefore, patchy, diffused, or irregular in distribution. Late in the process, when the false hypertrophy has disappeared, the fragmentation, degeneration, and absorption of the true sarcous elements are most marked.

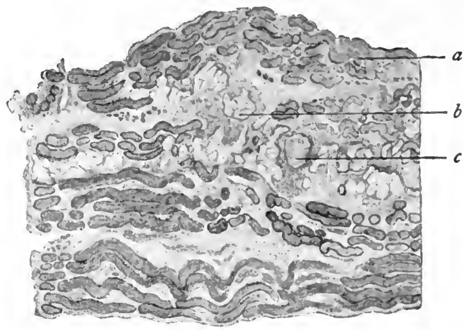


FIG. 385.—SECTION TAKEN FROM THE GASTROCNEMIUS MUSCLE OF A CHILD SUFFERING FROM PSEUDOHYPERTROPHIC MUSCULAR PARALYSIS; FIXED IN FLEMMING'S SOLUTION AND STAINED WITH HEMATOXYLIN AND EOSIN. (Specimen lent by Dr. Harris.)

a. Muscle-fibers. *b.* Fibrous and fatty tissue. *c.* Blood-vessel the lumen of which has been occluded by fibrous tissue. The disarrangement of the muscle-fibers and the increase in the fibrous and fatty tissues are well shown.

A form of muscular atrophy occurs unassociated with the preliminary

[1] Gowers, "Lancet," April 12, 1902; also "Brit. Med. Jour." July 12, 1902, p. 89. Eshner, "Phila. Med. Jour.," June 7, 1902.

stage of pseudohypertrophy, and appearing more frequently in young adults than in children. Two types of the lesion have been described—(1) one by Erb and (2) one by Landouzy and Déjerine. As to the relation of the two forms, opinions differ; some maintaining their identity, and others holding that they are distinct processes. While to a certain extent different muscular systems are involved, the lesions in the affected muscles are not unlike. In the form described by Landouzy and Déjerine the wasting begins in the face, and next involves the muscles of the shoulders and arms. This peculiarity has led to its being called the *facio-scapulohumeral* type. In that form of muscular dystrophy described by Erb the face is not affected. The pectoral muscles, trapezius, latissimus dorsi, biceps, triceps, brachialis anticus, and supinator longus, and later the muscles of the lower extremity, are involved. On section, the muscles may have lost their normal color, and are largely composed of fibrous and fatty tissue. The remaining muscle-fibers are small; at first striation is retained, but later it disappears. It is usually held that the initial changes are in the muscle-fibers and that the increase of connective tissue is secondary. In many cases, however, the reverse seems to be true. No secondary lesion in the cord or ganglia has been recognized.

Fig. 386.—Progressive Muscular Dystrophy, Erb Type. (From "Pennsylvania Medical Journal," March 1898; report by Dr. Theodore Diller, to whom the author is indebted for the illustration.)

The atrophy of the muscles forming the shoulder girdle, the pelvic girdle, and the arms and thighs is well shown. Notice the marked lordosis. The muscles of the forearm and calves are not involved.

True **hypertrophy of muscle** is usually dependent upon an increased demand for work accompanied by sufficient nutrition. It is most highly developed in athletes, where systematic training has brought the muscles to the highest degree of functional power. Occasionally, the hypertrophy may be restricted to certain groups of muscles, and may, in these cases, be dependent upon some special work thrown upon them, as is seen in the muscles of toe-dancers and in artisans in whom certain groups of muscles are brought

particularly into play. A certain amount of muscular hypertrophy is also observed in Thomsen's disease (*congenital myotoma*).

A typical example of hypertrophy resulting from increased work is seen in valvular disease of the heart. (See p. 512.)

Hemorrhage into the muscles or hematoma of muscle results from injury, either direct, as in bruising or wounds, or from tears in the muscle due to violent contraction, as in tetanus. In typhoid[1] and other infectious diseases rupture sometimes occurs from slight muscular exertion. The sternocleidomastoid muscle is occasionally ruptured during the delivery of a child. The interstitial hemorrhage and laceration of fibers are sometimes followed by cicatricial thickening and subsequent contraction; usually, however, the blood is absorbed without permanent alterations in the muscle. Muscle ruptures occurring in delivery of the infant frequently give rise to permanent disability and constitute an important cause of **congenital wry-neck.**[2]

Of the **infiltrations** occurring to muscles, *pigmentation* is deserving of mention as being frequently associated with various atrophic processes. The infiltration is also observed in old inflammatory areas and in the neighborhood of chronic infectious processes. *Fatty infiltration* of muscle is seen in obesity, in the overfed, and sometimes in alcoholics; occasionally it is localized to certain groups of muscles, in which case the deposit may be sufficient to justify calling the condition **diffuse lipoma**[3] of muscle. Occasionally, acute inflammatory lesions of the muscles is followed by the deposit of considerable calcareous material. *Amyloid infiltration* is rare; it is occasionally observed in the neighborhood of inflammatory processes, and at times is seen independent of existing inflammation. The muscles of the tongue and larynx are said to show the changes most frequently. The deposit is between the fibers.

Degenerations.—Of the various degenerative changes in muscles, *cloudy swelling* and *fatty degeneration* are most common. The alterations seen in the fibers are not different from those already described in the heart muscle. (See pp. 242, 243, and 491.) In edema *vacuolization* or *hydropic degeneration* of the fibers occurs. It is usually manifested by the appearance of vacuoles within the fibers. These vacuoles are sometimes numerous and small, and in other instances they are large and single. (See p. 245.) Distinct separation of the contractile substances (fragmentation) frequently follows degenerative changes, and an interstitial fibrosis is also occasionally present. Hyaline degeneration (p. 247), accompanied or preceded by coagulation necrosis (p. 251) of the muscle-fibers, is observed in the course of infective diseases—conspicuous among which may be mentioned typhoid fever, in which disease the abdominal muscles most frequently show the change.

Myositis or inflammation of muscle results from a number of causes and occurs in several forms; wounds, tears, and hemorrhages into the interstices of muscle are attended by an inflammation which, in the absence of infection, is usually slight and terminates in repair. Gowers[4] believes that lumbago and certain forms of muscular rheumatism, stiff

[1] Pérochaud, "Gaz Méd. de Nantes," 1904, No. 38, and Pérochaud and Doncet, "Gaz. Méd. de Nantes," Sept. 17, 1904.

[2] Maass, "Zeit. f. Orthopädische Chirurgie," 1903, xi, p 416.

[3] Debuck and L'Moor, "Belgique Med.," Nov., 1900.

[4] "Brit Med. Jour.," Jan. 16, 1904, p 117.

neck and pleurodynia, are inflammatory conditions affecting the interstitial structure of muscle, for which condition he proposes the name **fibrositis.**

Acute myositis may be simple or suppurative; there is also a form in which a number of muscles are involved, called **polymyositis.** In **hemorrhagic myositis** the inflammation is accompanied by hemorrhages into the affected muscles. In **acute nonsuppurative myositis,** or **simple myositis,** the muscle is swollen, tender, commonly rigid, on section dark and may contain areas of hemorrhages. Microscopic examination shows the muscle-fibers swollen and often necrotic and fragmented; edema and, in acute cases, fibrin are present in the interstitial tissue which is also infiltrated by varying numbers of mononuclear leukocytes.

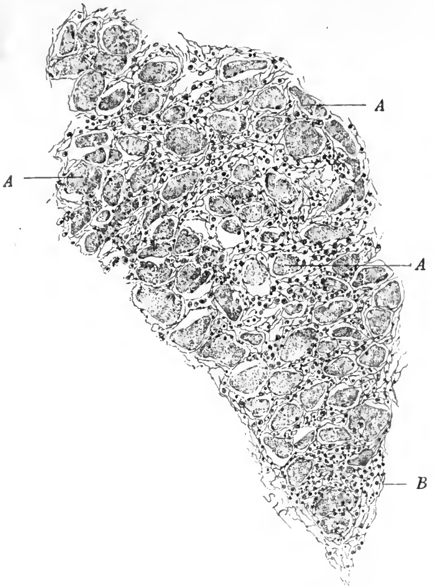


FIG. 387.—INTERCOSTAL MUSCLE, ACUTE, NONSUPPURATIVE, INTERSTITIAL MYOSITIS.

Transverse section, from a case of epipneumonic pleurisy, showing dissociation of fibers, interfascicular leukocytic infiltration, and slight fibrin formation. Tissue fixed in Zenker's fluid; hematoxylin and eosin stain.
A, *A*, *A*. Granular and fragmented muscle-fibers. *B*. Accumulation of leukocytes and fibrin around, and extending between the muscle-fibers. In some areas the change is more marked than in others, and at points many polymorphonuclear leukocytes can be seen.

Acute suppurative myositis results from direct infection, as by wounds, or propagated suppurative lesions contiguous to the muscle, rarely by lymphogenous extension and occasionally the bacteria are deposited from the blood. Hematogenous infections of the muscles are commonly associated with some form of infection in which bacteria are expected to enter the circulation. The condition has been observed in typhoid, although in most instances typhoidal myositis stops short of suppuration; in Scannell's[1] case the rectus abdominis muscle was involved and the condition was mistaken for appendicitis. Suppurative polymyositis usually accompanies pyemia, septicemia, and other forms of bacteremia; it has been observed in gonorrhea.[2] The **myositis infectiosa,** especially frequent in Japan, belongs with this group; of the thirty-four cases recorded by Miyake,[3] all but one terminated in suppuration; cultures disclosed the Staphylococcus aureus in thirty-three of the patients; in one case the lesions were due to the streptococcus. The alterations in the muscle, constituting a conspicuous part of Ludwig's angina (p. 679), are manifestations of an **acute diffuse interstitial suppurative myositis** with secondary degenerative and necrotic changes in the muscle-

[1] "Boston Med. and Surg. Jour.," Nov. 26, 1903.
[2] Harris and Haskell, "Johns Hopkins Hosp. Bull," Dec., 1904. Bisquet and Bichelonne, "Revue de Méd.," May 10, 1904.
[3] "Mitth. a. d. Grenzgebiet. d. Med. u. Chir.," 1904, Bd. xiii, p. 155.

fibers. The same lesion may result from similar infections due to other causes. In such conditions the interstitial tissue contains varying numbers of polymorphonuclear leukocytes, serum, and fibrin, and destructive lesions of the muscle-fibers are constantly present; the last are essentially necrotic. **Localized** or **circumscribed suppurative myositis,** or **muscle abscess,** does not differ essentially from other abscesses, although sometimes it extends with great rapidity. It may result from infection primary in the tendon-sheaths or extension from para-articular suppuration.

Acute polymyositis, also called **dermatomyositis,**[1] or, when the mucosæ are also affected, dermato-mucoso-myositis, is probably an infection, although Steiner concludes that the cause remains undetermined. This observer has been able to collect twenty-eight cases, three of which

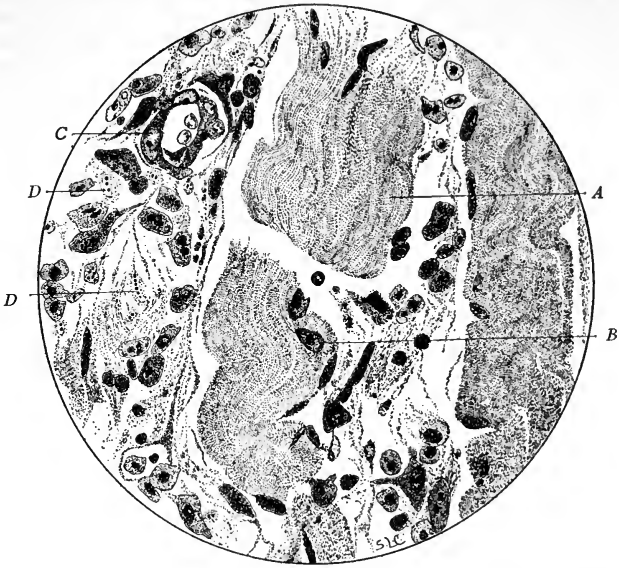


FIG. 388.—MYOSITIS, ACUTE DIFFUSE SUPPURATIVE. CASE OF LUDWIG'S ANGINA.
A. Fragmenting muscle-fiber. *B*. Same containing myoclasts. *C*. Vessel with swollen endothelium. *D*, *D* Pneumococci to which the process was due.

occurred in the United States. A few or many muscles may be involved; they are swollen, red or pale yellow, sometimes streaked with gray or reddish striæ, and in consistency may be firm, or soft and boggy; hemorrhages are occasionally present. Histologically the fibers are granular, hyaline, sometimes fragmented, and occasionally fatty. Interstitial swelling and lymphoid accumulations occur; the spleen is soft and enlarged and bronchopneumonia is sometimes present. Subcutaneous edema and cuticular inflammatory changes are conspicuous clinical features of the affection. Stomatitis, with or without ulceration, and angina have been observed. In some cases the condition is accompanied by polyneuritis.

[1] Steiner, "Jour. of Exper. Med.," 1905, vol. vi, p. 407. Strong, "Deut. Zeit. f. klin. Med.," 1904, Bd. liii. Bauer, "Münch. med. Woch.," Jan. 26, 1904, No. 4.

Parasitic myositis is a local lesion resulting from the deposit of animal parasites in the muscle; in trichinosis (p. 204) it is a polymyositis and is usually accompanied by eosinophilia (p. 417).

Chronic interstitial myositis,[1] also called *fibrous myositis*, *sclerosing myositis*, *myositis fibrosa*, and *myositis with contraction*, is a protracted inflammation of muscle attended by the formation of fibrous tissue and progressive atrophy of the fibers of the affected tissues. The condition may be primary, in which case it is called idiopathic, or, when due to trauma, ischemia, or persistent local irritation, the lesion is spoken of as secondary interstitial myositis. Little is known concerning the changes occurring in the muscles in the so-called chronic muscular rheumatism, but in some instances the structural alterations represent mild grades of this productive interstitial myositis; the fibrosis is rarely, if ever, marked in rheumatic cases. When myositis fibrosa is progressive, the affected muscles waste, become firmer and contracted, distorting the limb, and fixing the joints, which later may ankylose. Batten has shown that granular and fatty degenerations affect the muscle fibers in direct proportion to the extent of the fibrosis. In some cases the fibrous tissue is deposited in islands, justifying the name insular or nodular fibrous myositis. The condition has been mistaken for neoplastic formation, and in one case the scapula was excised under the conviction that the process was sarcomatous. The enlargement of the muscles seen in the early stages, before degenerative changes occur in the fibers, is often confusing. At this time the microscope shows an irregular and rarely abundant infiltration by mononuclear leukocytes; later these cells are inconspicuous or absent and the interfibrillary deposit is almost exclusively fibrous tissue, which, in some cases contains considerable fat. Associated obliteration of the vessels is often found and is probably the cause of some cases.

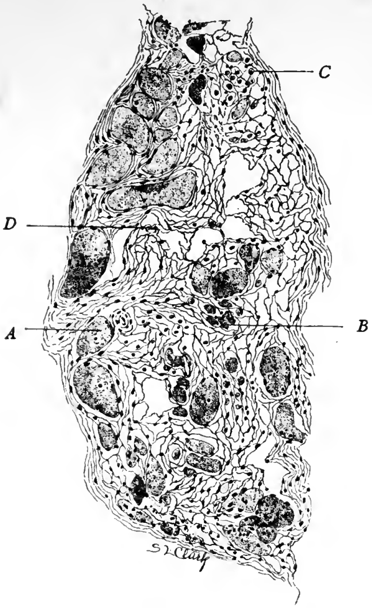


FIG. 389.—INTERCOSTAL MUSCLE.

Transverse section, from a case of suppurative pleurisy of several months' duration, showing advanced fibrosis and lipomatous change. Tissue fixed in Zenker's fluid; hematoxylin and eosin stain.

A. One of several granular fibers, some of which are fragmented and undergoing absorption. *B*. A small group of greatly shrunken muscle-fibers. *C*. Relatively large mononuclear cell, not very abundant, but commonly associated with fibroblastic elements. *D*. The leader from this letter passes between two imperfectly presented fat bodies, a number of which are present in the newly forming or formed fibrous tissue. The fat content is scanty in the particular field from which this drawing was made.

Under the name **chronic ossifying myositis (myositis ossificans)** has

[1] Biggs, "Univ. of Penna. Med. Bull.," Dec., 1901. Batten, "Clin. Soc. of London," Nov. 13, 1903; "Lancet," Nov. 21, 1903. Pernice, "Rif. Med.," Oct. 19, 1904, No. 42. Coplin, "Path Soc. of Phila.," Jan. 28, 1904; "Amer. Jour. of Med. Sci," May, 1904.

been described an affection the inflammatory character of which has been indisputably established. The inflammation is associated with the production of calcareous deposits between, in, or near the muscles. The fact that the muscle-fibers show but little alteration, even late in the process, indicates that the disease essentially involves the connective tissue. In some cases the bony deposit follows injury, particularly slight repeated bruisings; in other instances no history of trauma can be elicited. There is usually proliferation of the connective tissue of the muscle, which progresses to the formation of bone, very much as is observed in similar proliferative processes affecting the periosteum. As the structural changes are not restricted to the muscle, but occur also in the fasciæ and tendons, all sorts of irregular osseous or osteoid collections can be produced. The disease pursues a chronic course, usually beginning in the muscles of the

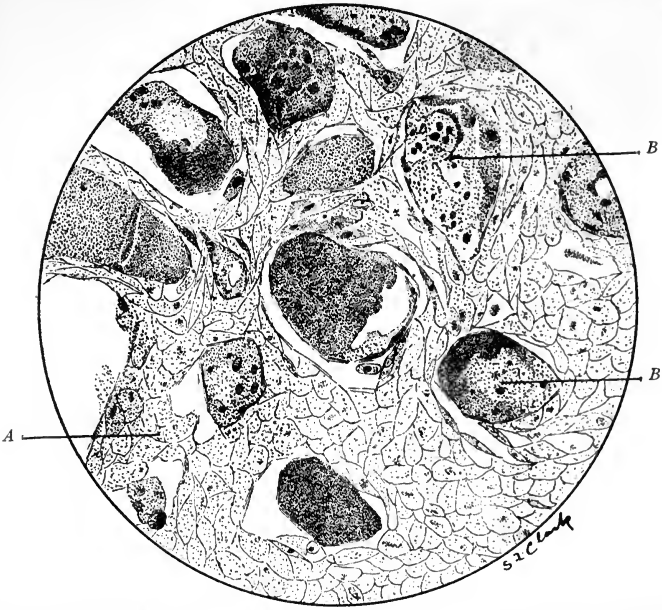


FIG. 390.—OSSIFYING MYOSITIS. *A*. Matrix of osteoid tissue. *B*. *B*, Fragmenting muscle-fibers.

neck or back, to which it may remain restricted. Later, it sometimes manifests a tendency to progress and involves all the muscles of the trunk, with ankylosis of joints, rendering the limbs and trunk stiff, or eventually entirely rigid. The bony collections are irregular, consisting of flakes and spicules, which later often coalesce and form larger masses. Various theories[1] intended to explain the condition have been advanced. The new bone has been attributed to ectopic periosteum, congenitally out of place or detached by muscle contraction or trauma; some believe the affection is a definite dystrophy allied to pseudohypertrophic muscu-

[1] Taylor, "Annals of Surgery," June, 1903. Renzi, "Gaz. degli Ospedali ed delle Clin.," Sept. 20, 1903, p. 1187. Busse and Blecher, "Deut. Zeit. f. Chir.," June, 1904, Bd. 73. Cahier, "Revue de Chir.," June, 1904, p. 827. Comby and Davel, "Arch. de méd. des enfants," Paris, July, 1904

lar atrophy. It has been regarded as neoplastic, and the resemblance to tumor formation is often striking; I have known two instances in which extremities were amputated under conviction that the enlargements were ossifying sarcomata. The histology is often confusing; the affected areas are infiltrated by mononuclear cells which strongly resemble those of sarcoma. Giant cells, apparently identical with such structures occurring in the marrow, are frequently present. Bone formation by the evolution of an osteoid tissue without the production of cartilage is the usual order followed; in some cases, however, cartilage is present. There is usually a cellular matrix containing fragmenting and degenerating muscle-fibers which later disappear. The osteoid tissue consists of granular substance in which calcification rather than true bone formation first takes place; later imperfect Haversian systems and more or less typical bone are produced.

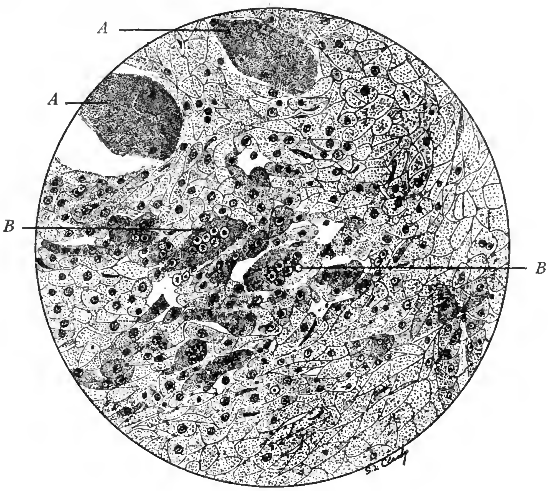


FIG. 301.—OSSIFYING MYOSITIS.
A, *A*. Fragmenting muscle-fibers. *B*, *B*. Giant marrow cells. The matrix in which *A* and *B* are situated is a granular partly calcified osteoid tissue.

Tuberculosis of muscle[1] is exceedingly rare; of all the tissues in the body, muscle seems most resistant to invasion and colonization by the tubercle bacillus, and often escapes virulent and wide-spread infection such as is observed in disseminated acute miliary lesions. There is little reason for believing that primary tuberculosis of a previously healthy muscle ever occurs. Secondary tuberculosis is usually due to direct extension from contiguous lesions. Plantard recognizes three forms of muscle tuberculosis: (1) The **tuberculoma,** which is usually caseous, but it may contain a large amount of fibrous tissue and resemble a gumma. (2) **Cold abscess,** which is really a more diffuse form of caseous tuberculosis of muscle, and is generally due to extension of osseous tuberculosis, arising in the bone to which the muscle or its sheath is attached. (3) **Tuberculous interstitial fibroid myositis** arising in muscles contiguous to tuberculous lesions and probably due to local dissemination of poisons produced in adjacent structures; this is the lesion observed in muscles lying next to tuberculous joints, glands, or bones. In addition to the foregoing should be mentioned occasional instances of definite miliary tuberculosis of muscle.

Syphilis of muscle[2] is of infrequent occurrence. An **acute nonsup-**

[1] Plantard, Thèse de Paris, 1901. Lejars, "La Sem. Méd.," June 1, 1904, vol. xxiv. No. 22; "Medical Press and Circular," June 22, 1904.
[2] Bigot, Thèse de Toulouse, 1901. Busse, "Arch. f. klin. Chir.," 1903, vol. 69, Nos. 1 and 2. Fordyce, "Jour. of Cutaneous Diseases," April, 1903.

purative diffuse interstitial myositis (Ricord) occurs during the secondary stage of syphilis, and it is possible that this forms the starting-point of a more chronic fibroid form, developing later in the infection. In both the acute and chronic types of syphilitic myositis the alterations in the muscle-fibers succeed the interstitial changes. Histologically the affected muscle is first infiltrated by mononuclear cells and later an excess of fibrous tissue is produced. The most common manifestation of muscle syphilis is the **gumma,** which in this structure does not differ from similar lesions occurring elsewhere (p. 179).

Leprosy and **actinomycosis** rarely involve the muscles.

Tumors of muscle, when primary, necessarily belong to the connective-tissue series. *Lipoma*, which may be circumscribed or diffuse, occasionally occurs; *fibroma* and *myxoma* have been observed. *Chondromata* are exceedingly rare. The bone formations of myositis ossificans (p. 794) are, by some observers, included with the neoplasms arising in muscle. Independent of such origin **osteomata** in this situation are infrequent. *Angioma*[1] is not an exceedingly rare tumor and may be mistaken for sarcoma. It is most frequent in the muscles of the extremities and is probably of traumatic origin. As a rule, the neoplasm is restricted to a single muscle, all of which may be involved. Paton reports an instance in which the entire gracilis muscle was affected. The angioma may be circumscribed or diffuse, simple, plexiform, or cavernous; the last is the usual form. Thrombosis, calcification, and transformation into sarcoma have been observed in angiomata of muscle. Katholitzky has reported an instance of lymphangioma of the muscles of the forearm. Sarcoma is probably the most common primary tumor of muscle, in which the neoplasm often proves extremely malignant. *Secondary cancer* and *secondary sarcoma* are frequently observed in the muscle.

Parasites of Muscle.—Trichinæ (p. 204), cysticercus cellulosæ (p. 197), and hydatids (p. 199) invade the muscles.

[1] Magarucci, "Il Policlinico," Nov., 1902. Rigaud, Thèse de Paris, 1903. Keeler, "Deut. Zeit. f. Chir," Sept., 1904, Bd. 74.

CHAPTER XV.

BONES AND JOINTS.

THE BONES.

Normal Structure.—Histologically, bone consists of a modified form of connective tissue presenting certain structural peculiarities in different bones and in different parts of the same bone. The long bones except at the articular ends, are covered by a membrane called the *periosteum.* This structure consists of dense connective tissue which is divided into two distinct layers. The outer layer affords attachment for the aponeuroses, tendons, ligaments, and fasciæ, with which it is practi cally continuous. It is comparatively rich in blood-vessels, some o which pass to the underlying layer and afford additional nutrition to the adjacent bone. As a result of its intimate association with the surrounding tissues, this layer of the periosteum is subject to the diseases, particularly the chronic infective processes, involving the adjacent structures. It is intimately connected with the underlying or genetic layer, from which it can not always be easily differentiated, the two forming a fairly uniform membrane. The outer layer is composed of dense fibrous tissue; the inner is richer in elastic tissue, and immediately adjacent to the superficial stratum of bone it contains, in varying numbers, osteoblastic elements, through the activity of which the circumferential growth of the bone is accomplished. The degree of adhesion between the inner layer and the bone proper varies. Besides the somewhat loose cellular attachment, the genetic layer is further secured in many localities by the presence of certain fibers that penetrate the compact portion of the bone, and also by the vascular communication between the two structures, through which, in part, the nutrition of both is maintained.

Immediately adjacent to the periosteum is the *compact portion* of the bone, while still deeper the supporting osseous structure assumes a spongy consistence, constituting the *spongy layer.* The quantity of compact tissue, as compared with the spongy, varies in different bones and is not uniform for all parts of the same bone. Thus, in the long bones there is a relatively thick, compact layer in the shaft, while the extremities are composed for the most part of spongy tissue covered by a thin shell of compact bone. The circulation of fluids within the compact portion of the bone is secured through the presence of two systems of channels—one of which is formed by Volkmann's canals and the other by the Haversian canals. The latter differ from the former in the fact that each canal constitutes the center of a lamellar system. Around this central space are arranged successive plates of osseous ground-substance, constituting the Haversian lamellæ. Between the latter are incomplete or partial lamellæ, called the interstitial lamellæ, while at the periphery, immediately under the periosteum, are the periosteal or outer circumferential lamellæ. Within the various lamellæ already mentioned are

smaller canals, called the lacunæ. The compact layer of the bone, projected inward toward the medulla, divides the inner area into irregular spaces, resembling the cavities found in a sponge, and hence this portion of the bone is called the spongy layer. In the meshes of this sponge-like tissue is held the bone-marrow, which further occupies the central canal or cavity of bone.

Bone-marrow.—Macroscopically, two kinds of marrow are recognized: (1) A *red marrow*, composed of a connective-tissue reticulum holding in its meshes certain cellular elements. (See Figs. 392 and 393.) Conspicuous among the cells of the marrow are the uninucleated

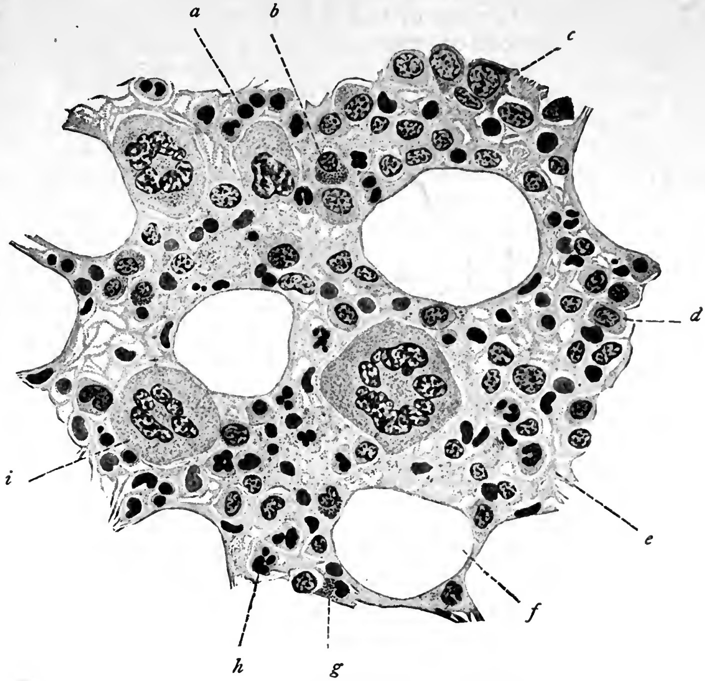


FIG. 392.—SECTION OF BONE-MARROW OF RABBIT, SHOWING THE DELICATE CONNECTIVE-TISSUE RETICULUM CONTAINING THE DIFFERENT ELEMENTS OF THE MARROW. ×400.—(*Schafer.*)

a, h. Hematoblasts. *b, g.* Eosinophilous cells (granule cells). *c, d.* Marrow cells (plasma cells). *e.* Connective-tissue reticulum. *f.* Fat space. *i.* Giant cell.

and multinucleated giant cells. Some of these cells attain a diameter three or four times that of the polymorphonuclear leukocyte, while cells tinctorially and structurally identical, but much smaller in size, are to be recognized as probably miniature myeloplaxes. Leukocytes are present in varying stages of development; if it is assumed that the white blood-cells are different throughout their life history, then it must be stated that all kinds of leukocytes are found in the bone-marrow. (See Table of Leukocytes, pp. 414 and 415.) The bone-marrow also contains a cell presumed to be the parent of the erythrocyte—called the *erythroblast.* The latter is nucleated; the nucleus possesses the usual affinity for basic dyes, while the cell cytoplasm gives, to a varying extent, the tinctorial

reaction of protoplasm containing hemoglobin. The amount of fat present in this type of marrow varies, but it is usually not abundant.

The (2) *yellow marrow* is composed largely of fat, and contains but few of the special cellular elements just described, and even these are not present in many localities.

The nutrition of bone is secured through an abundant blood-supply entering by means of the vascular twigs in the periosteum, to which reference has already been made, as well as by special nutritive branches. The vascular twigs from the periosteum pass through the Haversian and Volkmann's canals, communicating with branches from the bone-marrow having their origin in the nutritive vessels passing through the compact portion of the bone directly to the marrow tissue During the earlier periods of osseous growth a high degree of vascularity is necessary for the general nutrition of the bone as well as for its enlargement circumferentially and axially. In long bones possessing epiphyses there is usually an abundant vascular network between these structures and the shaft properly so called. At this line of junction the veins afford communication between the overlying tissues and

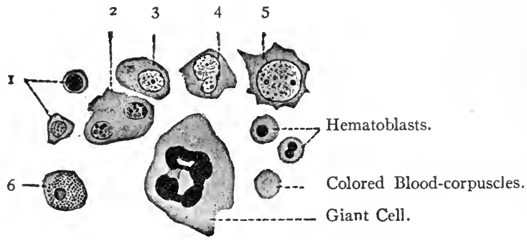


FIG. 393.—ELEMENTS OF HUMAN BONE-MARROW. × 600.
1 to 5. Various forms of bone-cells. 6. Eosinophilous cell.—(*Stöhr.*)

the bone-marrow, and hence infective or inflammatory processes attacking these special areas are extremely prone to involve, when arising externally, the medulla, and, when beginning in the marrow, can extend through the vascular disc to the para-osteal structures.

For a description of the process by which bone is developed the student is referred to standard text-books on histology and embryology. There is, however, one element deserving of special consideration, by reason of the fact that it has important bearings on morbid processes affecting the bones, and, even when pathologic, usually closely resembles the normal process. The condition to which reference is made is called **osseous resorption.** Bone is absorbed through the intervention of large nucleated masses of protoplasm which constitute one form of giant cells; these bodies apply themselves directly to the calcified matrix, within which they excavate small cavities, called *Howslip's lacunæ*. The particular cells accomplishing this function are called *osteoclasts*. Conclusive evidence as to the method by which they bring about the excavation in the calcified matrix is still wanting. It is reasonable, however, to assume that the cell secretes a material which liquefies and renders absorbable the dense structure; the process may therefore be regarded as closely allied to certain forms of phagocytosis (pp. 98 and

290). In growing bone, while the osteoclasts are gradually leading to osseous absorption in the interior, the exterior is receiving additional bone, laid down by cells already mentioned as present in the genetic layer of the periosteum, and called *osteoblasts*. This form of osteogenesis is called **osseous apposition.**

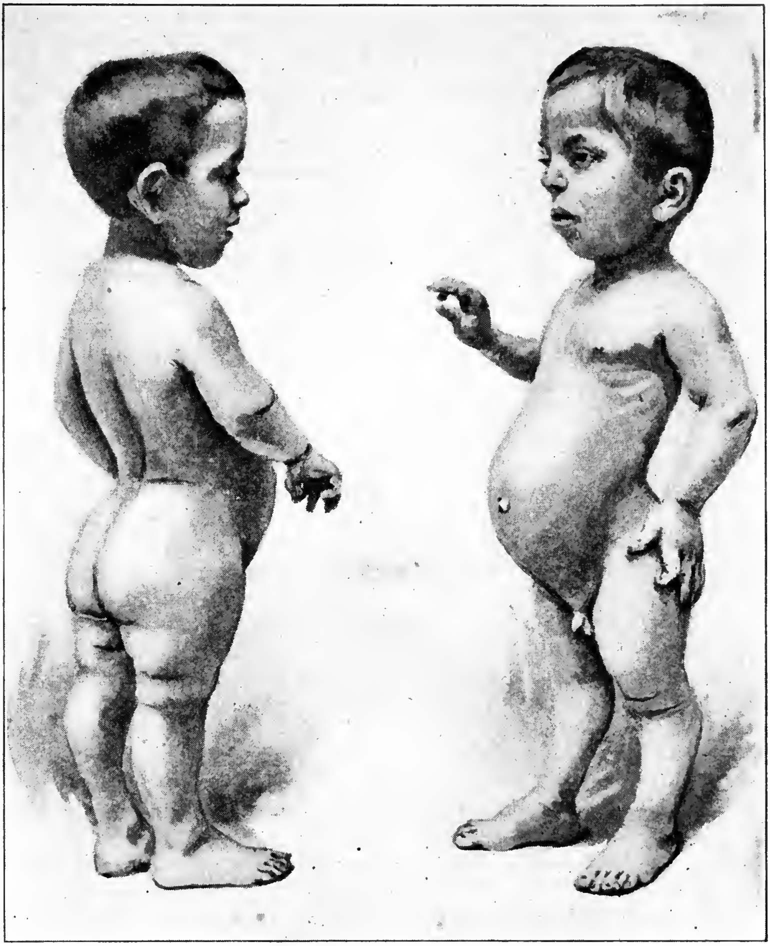


FIG. 394.—ACHONDROPLASIA.—(*Comby, courtesy of Dr. Richardson.*)

Malformation of Bone.—In the osseous skeleton many perversions of development occur. These are usually manifested by defective or perverted bone formation, which may be due to recognizable diseases of the blood-vessels or may arise without a demonstrable cause. As the larger part of the osseous skeleton is preceded by a stage of cartilage, any defect in the laying-down of this primary enchondral matrix (**achon-**

droplasia)[1] becomes manifest in the later growth and development of the bone. Aside from these defects in the initial process of osseous growth, there is to be recognized, later, certain malformations depending upon failure in the extent of growth; or it would be better to say the formation of the bone is not completed. Thus, arches may fail to coalesce, as is observed in the superior maxilla, where developmental arrest gives rise to harelip (see p. 673), cleft palate, etc.; or in the chest, resulting in the formation of a fissure that may extend the entire length of the sternum. A posterior fissural deficiency is sometimes present in the spinal column, the lamina of the vertebræ having failed to complete the arch that normally forms the posterior wall of the spinal canal, giving rise to the presence of a fissure, constituting a condition known as *rhachischisis*. (See Malformation of the Central Nervous System.)

Agenesis may be restricted to one bone, or even to a part of the bone, or it may be more extensive, involving the osseous structures of a large area. Sometimes the defective development is remarkably uniform, all the bones of the skeleton being influenced to approximately the same degree, giving rise to the typically symmetric and accurately miniature individual called the dwarf—**microsomia, nanosomia** (see p. 222). In other cases the arrest in growth is restricted to certain areas or to single bones, leading to asymmetry, one limb or one part of the pelvis or one side of the chest showing a development that approximates the normal and is far in excess of that attained by the opposite side.

Of the ultimate cause of these conditions little is known. Local arrests may depend upon morbid processes influencing the nutritive organs during developmental stages; prominent among the causes acting in this way may be mentioned rickets and syphilis. The deformities indicated are commonly attributed to inheritance, diseases of the thyroid gland, intrauterine conditions including the influences of heredity and maternal disease, and imperfect osteogenesis; it must be evident that such explanations are insufficient and unsatisfactory.

It is equally difficult to explain the remarkable overgrowth of bone occasionally observed. The fact that osseous overgrowth is sometimes associated with diseases of the hypophysis cerebri offers but little aid in our effort to solve this obscure problem. Possessing little information concerning the functions of the hypophysis, it is quite impossible, for the present at least, to infer the actual relation existing between morbid processes in this organ and the tissue overgrowth involving the bones and other tissues. In acromegaly a more or less uniform enlargement of many of the bones of the skeleton occurs. There is true increase in length and circumferential enlargement due to the deposit of osseous matter in the subperiosteal layers, either alone or associated with osteophytic excrescences.

Changes in the bone-marrow resulting from the influence of systemic conditions and often independent of local disease, properly so called, are now well known. Reference has been made to structural alterations affecting this tissue in pernicious anemia (p. 424) and leukemia (p. 427). Muir[2] and others have shown that certain medicaments increase the

[1] Hektoen, "Amer. Jour. of Med. Sci.," May, 1903. Poncet and Lereish, "Revue de Chir.," Dec. 10, 1903, p. 657. Balme and Reid, "Practitioner," Dec., 1904, p. 780.

[2] "Jour. of Path. and Bact.," Nov., 1901. See also Stockman and Charteris, "Jour. of Path. and Bact.," Dec., 1903, p. 202.

number of erythroblasts, and possibly in other ways stimulate the hematogenic functions of the medullary tissues. Henke has specially investigated the bactericidal properties of the marrow, and a number of observers[1] have demonstrated that it undergoes important changes in certain intoxications and many infections. In acute infections the leukocyte-forming function is usually stimulated, areas of necrosis are commonly present, and the phagocytic qualities of the marrow are increased. In chronic infections fatty marrow is sometimes replaced by the more cellular form and evidences of increased hematogenesis are occasionally marked.

Hemorrhage under the periosteum, giving rise to more or less detachment of the membrane, occurs in scurvy, and other blood dyscrasias, and in cephalhematoma; the last-named condition results from the trauma of labor. The extent of the hemorrhage largely depends upon its cause, and upon the resistance of the individual. In marked cases of infantile scurvy the periosteum may be dissected loose from the bone over a large area, so that the shaft of the femur, for example, may show a periosteal attachment at each end only, the intermediate area having been detached by the blood-clot. The immediate sequences and ultimate results of such hemorrhage largely depend upon the presence or absence of infection. When bacteria or bacterial products are excluded, death of the bone is usually averted, more or less absorption, and, later, organization of the effused blood taking place. In the presence of infection, suppuration with extensive necrosis, septicemia, pyemia, and death constitute the ordinary sequence of events.

Periostitis.—Inflammation of the periosteum may be *acute* or *chronic*, *simple* or *noninfective* and unassociated with the presence of bacteria, or it may be *suppurative.*

Acute Simple Periostitis.—Under this head must be grouped the more or less trifling inflammatory and reparative changes resulting from bruises and other injuries of the periosteum, and unattended by infection.

Under such circumstances the periosteum is swollen, and may be separated from the underlying bone by subperiosteal hemorrhage. The density of the periosteum militates against the occurrence of marked redness and injection, although they may be present. Quickly following the injury and hemorrhage, absorption of the blood begins; this is accompanied by a varying amount of proliferation of the connective tissue, including the genetic layer of the periosteum, with more or less leukocytic infiltration. The extruded blood is largely removed through the activity of phagocytes, and the resulting cellular accumulation proceeds to the formation of cicatricial tissue, which may become calcified or be converted into bone by the osteoblastic elements present in the periosteum.

Acute suppurative periostitis commonly follows trauma with infection, although mycotic lodgment in the periosteal structures may occasionally occur without any antecedent injury sufficiently important to be recalled

[1] Muir, "Trans Path. Soc. of London," 1902, vol. 53, p. 379. Graag, "La Presse Méd.," Aug. 8, 1903. Fränkel, "Mitteil. a. d. Grenzgebiet. d. Med. u. Chir.," Bd. xii, No. 4. Henke, "Arch. des Sci. biolog. de Saint-Pétersbourg," 1904, tome x, No. 2. Longcope, "Bull. of the Ayer Clin. Lab. of the Penna. Hospital," Jan., 1903, No 2.

by the patient at the time when symptoms first manifest themselves. It may be secondary to osteomyelitis.

The organisms most frequently associated with this condition are the pyogenic cocci, the colon bacillus, the pneumococcus, the gonococcus, occasionally the typhoid bacillus, and less frequently other microbes. Bacteria may reach the point of colonization by means of the blood, as their frequent presence in the circulation is now conceded by all who have studied the question. In other cases the infection is direct, as by trauma. The periostitis just described may be converted into the suppurative form by the lodgment of bacteria at the newly evolved area of diminished resistance. When a preinfective stage is present, the changes during that period are those already described as present in the acute simple form.

With the inception of infection, coagulation and liquefaction necroses promptly occur and polymorphonuclear leukocytes accumulate in large numbers, converting the inflammatory exudate into pus. The disposition of the process is to extend, usually involving more or less of the underlying bone, which is further influenced by the fact that the nutrition to its periphery is imperilled by separation of the periosteum. The density of this fibro-elastic membrane does not favor the easy escape of infective material, and hence the latter frequently detaches the periosteum for some distance beyond the original area of involvement. The rapidity and the extent of the process depend upon the susceptibility of the individual and upon the activity or rather the virulence of the infective agent. Thus, in debilitated patients trifling initial lesions may be followed by the gravest consequences, and when lessened protective powers are associated with virulent infection, extensive necrotic processes commonly ensue. Occasionally, the suppuration is circumscribed, the bacteria are destroyed, and an area of healed-in suppuration is formed. In other instances perforation of the periosteum takes place and a **paraosteal suppuration** follows. The extension of the infective processes may be rapid, often surrounding a contiguous joint and inducing a periarticular abscess. In other instances the condition leads to separation of the epiphysis, and even penetrates the joint, or from the juxta-epiphyseal line, may involve the medulla of the bone, inducing thereby a more or less typical osteomyelitis. Occasionally, the infective process is further complicated by the presence of hemorrhage, and to this form has been given the name **hemorrhagic periostitis.**

A chronic inflammatory process occurs in the periosteum, and has been called **fibrous periostitis.** It is at times to be regarded as a consequence of the simple acute periosteal inflammation; in other cases syphilis appears to be the cause; and in still other instances it is secondary to inflammatory and infectious diseases primarily in adjacent tissues. It is essentially chronic from the beginning, lasting for years, is not usually associated with marked symptoms or prominent tissue changes, and but rarely is transformed into a more grave type of periosteal disease.

The periosteum is thickened, extremely dense, and firmly attached to the underlying bone. Calcareous deposits may be present in the newly formed sclerotic tissue, and may be projected into attached tendons and fasciæ, giving rise to calcified masses closely resembling the results of the so-called **ossifying periostitis.** (See Figs. 399 and 400.) In the

latter condition there are bony outgrowths (osteophytes), which are projected into the adjacent tissues and sometimes form masses of unusual size. Rarely, the outgrowth is uniform, increasing the diameter of the bone; and, as it is unassociated with a corresponding increase in length, thickening and other deforming processes may result. The compact layer always appears considerably thicker than the normal bone. The formation of new tissue, both osseous and fibrous, has led to the condition being called **chronic productive osteoperiostitis.**

Closely allied to the suppurative inflammations of the periosteum is **periostitis albuminosa.** That the inflammation is essentially of infective origin is indicated by the frequency with which pyogenic organisms are found in the exudate; and that the infection differs from the ordinary infective processes in bone is further indicated by the course of the disease and the character of the discharge. The inflammation is not usually restricted to the periosteum, but involves the adjacent compact portion of the bone (osteitis) or the bone-marrow (osteomyelitis), and in some cases both. The discharge often manifests but little resemblance to pus, although it frequently contains pyogenic organisms and a considerable number of polymorphonuclear leukocytes. It is rich in albumin and contains some sugar and the usual bone salts. Ordinarily, it is fluid in character, although it may be semifluid, and on standing sometimes coagulates as a whole or may be separated into layers, the uppermost of which appears oily, with a varying amount of coagulation in the strata below. Occasionally, the inflammatory and necrotic processes are partly encapsulated.

FIG. 395.—CHRONIC PRODUCTIVE OSTEO-PERIOSTITIS.

Anemia, hyperemia, and **congestion** of bone are of little pathologic importance when considered as simple processes. The absence of elasticity prevents any unusual degree of vascular distention, and therefore limits the possibility of abundant arterial influx or venous accumulation. This statement does not imply that the amount of blood within the bone can not vary. Variations, however, are slight, and even with extensive inflammatory processes the evidence of vascular distention may be wanting. In general anemia, and when obliterative lesions in the blood-vessels, such as result from syphilis, have affected the arteries leading to the bone, a varying amount of anemia may occasionally be recognized. During the active stage of osseous evolution and growth, and before the completion of development, the blood-supply to the bones is relatively abundant. With completion of the osseous matrix, and

later, when marrow transformation has been accomplished, the amount of blood present in the bone is greatly diminished. During various processes the blood-supply is manifestly increased, and retardation of exit may intensify vascular distention, but the inelasticity of the Haversian canals more or less limits even inflammatory hyperemia. The changes in the bone-marrow seen in pernicious anemia have been regarded by some authorities as evidence of hyperemia. The conversion of the fatty marrow into the richly cellular marrow, as is sometimes seen in that disease, as well as in leukemia, certainly implies an increased blood-supply; but here the increased supply of blood constitutes a part of the local formation of new marrow, and is scarcely to be considered, in the present state of our knowledge, as a primary medullary process.

Hypertrophy of Bone.—In giants the extensive overgrowth of bone is regarded by some as essentially a process of hypertrophy. As is well known, this is at times remarkably symmetric and universal; in other instances the osseous overgrowth is restricted to one or more bones. and sometimes to the bones of a single member or to a single bone. The cause is unknown.

Acromegaly,[1] or **pachyacria,** is a disease associated with increase in thickness and length in the long bones, with more or less alteration in many of the small bones. That the flat bones are similarly affected is shown by the increase in size of the facial sinuses. The lower jaw increases in length and thickness (prognathous jaw), and may be projected so far forward as no longer to articulate with the superior maxilla. The osseous overgrowth is usually symmetric. The spine suffers a varying degree of dorsal kyphosis. In many cases the pelvic bones and the sternum are thickened; the diameters of the clavicles are increased and sometimes these bones are slightly elongated. The anteroposterior diameter of the chest is augmented as a result of the lengthening of the ribs and posterior curvature of the spine. The slight bulging backward of the spine and projection of the sternum forward, with the drooping head and prognathism, constitute the *ape-like deformity* of this disease. The bones of the hand are enlarged and slightly lengthened, giving rise to the *battledore hand* presumed to be quite characteristic of acromegaly. In acromegaly the hypophysis cerebri frequently shows some abnormality: it is sometimes the seat of a tumor, while in other cases the enlargement seems to be proliferative in character. The constancy with which changes are found in the hypophysis would naturally lead to the belief that this organ is the seat of the primary lesion, but similar, if not identical, alterations have been found in the pituitary body without the osseous phenomena of acromegaly. Nearly fifteen years ago Cunningham expressed the conviction that there was some relation between acromegaly and giantism, a view that has been steadily gaining ground. Giants frequently develop acromegaly, and it is probable that, whatever may be the cause of pachyacria, if it act prior to ossification of the epiphyses a giant is produced; if its influence be delayed until the epiphyses are united, acromegaly results. When the causative factor continues to operate, the giant finally develops some of the phenomena of acromegaly. There is no adequate reason for placing acromegaly with

[1] Bassoe, "Jour. of Nerv. and Mental Disease," Oct., 1903, p. 596. Launois and Roy, "Études Biologiques sur les Géantes," Paris, 1904. Cunningham and others, "Brit. Med. Jour.," Nov. 19, 1904, p. 1379.

diseases of the bones, as many of the soft tissues are equally involved; the viscera are commonly enlarged. It is probable that leontiasis ossea and **hemihypertrophy of the face** are processes closely allied to acromegaly, although at present we can in no way designate the character of the relationship.

Pulmonary hypertrophic osteoarthropathy[1] is a condition presenting some of the characters of acromegaly, but is probably a distinct affection. The club deformity of the hand is absent in acromegaly and the process is symmetric. In the disease under consideration the bones of the cranium are not involved. Marie, who first described the disease, believed it was due to the absorption of some substance from the lungs

Fig. 396.—Acromegaly. (Case reported by Lackey.)
Prominence of the nose with broadening of the alæ, external strabismus, prognathism, battledore hands, unusual increase in the length of the long bones (height of patient, 8 feet 6 inches), dorsal kyphosis, and marked muscular wasting are present in this case. The enormous length of the arms can be appreciated when it is stated that the patient's reach is 8 feet 9 inches; from crotch to heel the measurement is 4 feet 10 inches.

and pleura, the seat of an inflammatory process; he therefore called the disease *osteoarthropathie hypertrophiante pneumonique*. Godlee believes that a number of conditions are included under the one name; in his patient the symptoms of pulmonary osteoarthropathy disappeared after a long-standing empyema had discharged through a bronchus; the toxic nature of the affection is generally accepted.

A peculiar form of bony overgrowth is seen in **leontiasis ossea.** In this condition there is a symmetric enlargement of the facial bones.

[1] Janeway, "Amer. Jour. of Med. Sci.," Oct., 1903. Symes-Thompson, "Royal Med. and Chir. Soc.," Jan. 12, 1904; "Brit. Med. Jour.," Jan. 16, 1904, p. 134. Wynn, "Birmingham Med. Review," April and May, 1904.

The lower jaw is but slightly involved, while the bones of the trunk and extremities escape.

Aside from the conditions just described, there is occasionally observed evidence of osseous overgrowth that can not be properly considered with any of the foregoing conditions. As an example of this morbid condition may be cited certain local overgrowths of bone closely resembling tumors. These are sometimes projected from the compact

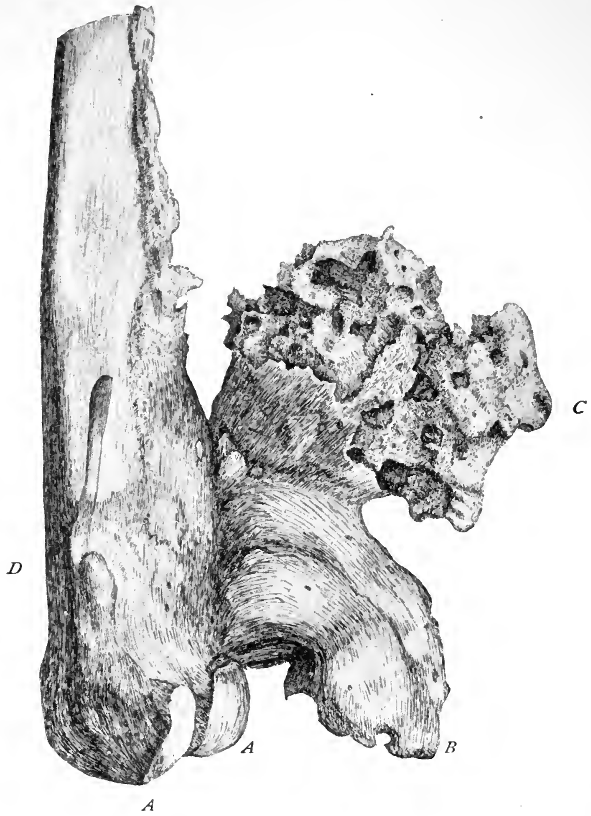


FIG. 397.—OSTEOPHYTES ON THE POPLITEAL ASPECT OF THE LOWER END OF THE FEMUR.
A, *A*. Articular surfaces. *B*. Compact osteophyte. *C*. Spongy osteophyte undergoing caries as a result of ulceration of the overlying soft parts and extension of infection to the bone. To the right of *D* is a spicular osteophyte and just below is a boss, evidently illustrating an earlier stage in osteophytic growth.

portion of the bone into the marrow cavity, constituting **enostoses;** more commonly growths upon the surface of the bone extend outward into the adjacent tissues; when small, these are called **osteophytes,** and if large, **exostoses.** Féré and Deniker[1] have called attention to symmetric exostoses for which there is no satisfactory explanation. When arising purely from the periosteum, and particularly when the origin is from the superficial layer, which has feeble bone-producing

[1] "Revue de Chir.," April 10, 1904, p. 544.

powers, these masses may be movable. Under such circumstances they are sometimes called **periostoses.** The growth of bone along the course of tendinous attachment is by some regarded as a form of hypertrophy. The osseous overgrowth resulting from inflammation, infection, and injury had probably best be considered with those processes. The hyperplasia resulting from the administration of such agents as arsenic and phosphorus merits no special consideration.

Atrophy of Bone.—Occasionally, atrophic processes begin in the osseous layer adjacent to the medulla, or in the Haversian lamellæ, and progress toward the periphery, constituting what is termed *eccentric atrophy.* On the other hand, the process may begin immediately under the periosteum, lessening the circumference of the bone, and in this form it is called *concentric atrophy.* In other forms of atrophy the osseous absorption occurs along the lines of the Haversian canals, and also involves, to a varying degree, the spongy layer. As a result of the widening of the Haversian canals, the bone appears spongy or porous, and the condition has received the name **osteoporosis;** the absorption following the course of the Haversian system has led to its being known as *Haversian atrophy.* As the disease is usually associated with conversion of the marrow into fatty tissue, it has been termed—probably incorrectly—fatty degeneration of bone. *Senile atrophy*[1] attacks more particularly the vault of the skull the scapula, and the pelvis—in other words, the flat bones. It is also seen in the inferior maxilla, and is often conspicuous in the alveolar process. As a result of eccentric and concentric atrophies the strength of the long bones may be materially lessened (**fragilitas ossium**[2]), favoring the occurrence of fractures. Disease and injuries involving the spinal cord and nerve-trunks are sometimes followed by atrophic processes, *neuropathic atrophy,* particularly in the long bones at or near the articular extremities. Injury and disease of contiguous structures or the bone itself are sometimes attended by atrophy; when due to the first-named cause, the condition is called traumatic atrophy,[3] and when resulting from inflammation, inflammatory atrophy.[4]

Pressure atrophy of the bone commonly results from constantly applied pressure, even of a moderate degree. Pressure of cicatrices, rapidly growing tumors, aneurysm, and fluid accumulation in cavities surrounded by bone, as in the air sinuses of the face, may be mentioned as causes of pressure atrophy. The aneurysm shown in figure 266, page 532, had caused pressure atrophy of the bodies of the vertebræ. A condition closely allied to pressure atrophy is the osseous resorption resulting from tumor formation or chronic infectious processes in the interior of the bone, as not infrequently occurs in the inferior maxilla, where neoplastic destruction of the interior is accompanied by continuous periosteal proliferation and external apposition. A similar condition is at times observed in the long bones as a result of tumors originating in the medullary space. Under such circumstances the bone may assume enormous proportions. The femur, for example, is sometimes

[1] Weber, "Brit. Med. Jour.," Jan. 21, 1905, p. 129.
[2] Biggs, "Univ. of Penna. Med. Bull.," Feb., 1903. Smith, "Brit. Med. Jour.," Oct. 3, 1903, p. 824.
[3] Imbert and Gagnière, "Bulle. Officiel de la Soc. Française d'Electrotherapie et de Radiologie," July and Aug., 1904.
[4] Sudeck, "Deut med. Woch.," May 8, 1902.

so enlarged that it measures from 12 to 15 cm. in diameter and may possess externally a layer of compact bone varying in thickness, but rarely approaching 0.5 cm.

Halisteresis is probably not a true atrophic process, although it is usually considered as one of the forms of osseous atrophy, and consists, for the most part, in the removal of the lime salts with subsequent changes in the osseous matrix. Occasionally it is a more or less local affection occurring in the neighborhood of some invading processes, or it may be general, in which case it constitutes the disease called **osteomalacia, mollities ossium** or **malacosteon.**

While osteomalacia[1] is a disease of adults, juvenile and senile forms occur. It is most frequently observed in females, and is recognized as one of the possible complications of pregnancy. Lactation, particularly when prolonged, is believed to be a determining factor. The fact that it is endemic in certain localities has led many to believe that it is infectious in origin; Moussu and Charrin have apparently proved that osteomalacia is transmissible. In the puerperal form it is first manifest in the bones of the pelvis, to which structure it may be confined; in other cases it begins in the bodies of the vertebræ, and the first evidence is the occurrence of lordosis, kyphosis, or scoliosis. The bone-marrow is hyperemic, and may contain areas of hemorrhage. It is usually richly cellular, and sometimes contains cysts. When advanced, the bodies of the vertebræ "may be squeezed out like a sponge," and the ribs are easily bent inward. In the long bones the osseous wall is sometimes no thicker than a sheet of paper, and can be easily indented by the finger. The pelvic deformity is commonly quite characteristic: the acetabulum is pushed inward, the iliac crest is pulled outward, the promontory of the sacrum and the pubic articulation are thrust abruptly forward. Fractures occur, and may be repaired, even during the activity of the process.

Early in the disease the histologic changes are inconspicuous. The bone salts are removed, and usually appear in excess in the urine. The first solution of the lime salts appears to occur at the periphery of the trabeculæ and around the Haversian canals. The process may therefore be considered a decalcification of the bone, but later the decalcified matrix is in part absorbed; or it may be converted into a coarsely fibrous structure.

Inflammation of Bone.—As a rule, periostitis causes a certain amount of inflammation in the adjacent osseous structures, and inflammation of the bone, approaching the periosteum, implicates that membrane. The classification and subdivisions of bone inflammation embrace: (1) Inflammation of the compact portion of the bone or of the osseous structure properly so called—a condition termed **osteitis** or **ostitis;** (2) an inflammation originating in, or extending to, the medullary structures, and hence called **osteomyelitis.** Periostitis, osteitis, and osteomyelitis are frequently concurrent.

The most important of these bone inflammations is **osteomyelitis.**[2]

[1] Tashiro, "Ziegler's Beitr.," Bd. 34, H. 2, p. 220. Pierart, Thèse de Paris, 1904. Hönicke, "Berlin. klin. Woch.," Oct. 31, 1904. Thos. A. and D. J. Davis, "Annals of Surgery," Aug., 1904. Moussu and Charrin, "C. R. Soc. de Biol.," May 7, 1904, p. 778.

[2] Hencke, "Centralbl. f. Bakt.," Bd. xxxiii, H. 8, p. 697; and "Arch. de Sci. Biol.," 1903, vol. 10, fasc. 2. p. 171. Nichols, "Jour. Amer. Med. Assoc.," Feb. 13, 1904, p. 439. Durbach, "Münch. med. Woch.," Sept. 20, 1904, p. 1689.

The process is essentially an infection involving, at first, the softer and more richly cellular parts of the bone. The organisms most frequently present are the staphylococci, and usually the staphylococcus pyogenes aureus. In a certain percentage of cases the streptococcus is the infecting microbe. Osteomyelitis depending upon the presence of the pneumococcus, the Bacillus typhosus, the Bacillus coli communis, the bacillus of influenza, and occasionally other organisms, occurs. A true tuberculous osteomyelitis depends, of course, upon the tubercle bacillus. The portal of entry and the route followed by the invading organism vary in different cases. Compound fractures and wounds exposing the osseous tissues to bacteria-laden agents may be taken as a type of direct infection. In preantiseptic days the disastrous results of compound fractures were due to the introduction of bacteria and the occurrence of an initial osteomyelitis that rapidly became part of a general septic process. It has been abundantly shown, however, that direct infection is not necessary to the occurrence of osteomyelitis, as the bacteria may reach the bone in other ways. Injury of the bone favors the occurrence of infection by the production of a point of least resistance, in which bacterial colonization is readily accomplished. A solution of continuity in the skin, such as is afforded by an abrasion or a superficial wound, may offer sufficient facility for bacterial ingress. In other cases no such external atrium can be demonstrated. In these instances it is generally believed that the bacteria enter the circulation by means of the respiratory apparatus, or, probably in a larger percentage of cases, by the alimentary canal. The pharynx and tonsils are also known to be portals of entry. The disease is most common in the young, being especially frequent in adolescence. It occurs, however, in infancy, and less commonly in middle life or in old age. The frequency with which the young are attacked is probably owing to the character and abundance of the vascular supply to the growing bone and on account of the very frequent occurrence of injury. A special form of osteomyelitis[1] occurs in workers in mother-of-pearl.

Initially, the disease attacks most frequently the long bones—the femur, tibia, humerus, and bones of the forearm, in the order given. It may be first manifested in the periosteum (periostitis), reaching the medullary cavity through the Haversian canals or the juxta-epiphyseal disc. The latter point is sometimes the beginning, and, occasionally, the disease remains limited to this area, constituting a form of osteomyelitis known as **acute infectious epiphysitis.** The vascularity of this area and its richness in venous plexuses, as well as its liability to injury, render it unusually susceptible. Although the long bones are usually attacked, other osseous structures are by no means immune; the round bones of the carpus and tarsus, the flat bones of the skull, and the bodies of the vertebræ are sometimes involved.

With the entrance of the invading organism inflammatory processes are at once inaugurated. There is more or less vascular distention, associated with thrombosis of many of the vessels; rapid and extensive leukocytic invasion; coagulation necrosis, followed by liquefaction of the intercellular substance; and destruction of the tissue, leading to the

Courmont and Lesieur, "Lyon Méd.," Dec. 18, 1904. Bernard, "Trans. of Path. Soc. of London," 1903. Guvot, "Revue de Chir.," Feb. 10, 1904, p. 271.

[1] Broca and Tridon, "Revue de Chir.," Oct. 10, 1903, p. 421.

development of purulent foci. Coalescence of these areas of suppuration, as well as extension along the tract of the marrow, lead to rapid disintegration of this substance. The extent of damage depends, as in most cases of infection, upon the virulence of the invading organism and the activity of the protective forces. In some instances the latter are insufficient, and the entire narrow cavity of the bone yields before the rapidly advancing process. The inflammation reaches and involves the periosteum, which often becomes detached; the nutrient vessels are thrombosed, and death (necrosis) of a part, or of the entire bone follows. With inflammation of the epiphysis penetration of the contiguous joint may occur, followed by suppurative arthritis. This suppuration not uncommonly breaks through the periosteum, inducing a **paraosteal abscess** that burrows along the line of least resistance and eventually reaches the skin, through which it ruptures. The dead bone is called a **sequestrum.**

As a result of the septic thrombophlebitis, systemic dissemination of bacteria, with or without infective emboli, frequently induces the gravest form of septicemia or pyemia. The evidences of intoxication are sometimes pronounced, and death, from the overwhelming character of the poison, may precede gross evidence of the infective processes in the bone involved. Should the patient survive the more acute inflammatory phenomena, separation of the dead part, and attempted regeneration of the bone are sooner or later inaugurated. (See Caries and Necrosis, p. 812.)

In some instances the infective process is limited, constituting a condition spoken of as **circumscribed osteomyelitis** or **osteal abscess.** Such abscesses may be extremely minute, rarely exceed from 1.5 cm. to 2.5 cm. in diameter. They occur in the cancellous structures of the long bones, and are more common in the upper end of the tibia than in all other situations put together. Osteal abscesses of long duration are usually surrounded by a zone of sclerotic or indurated bone of the densest character, and after such effort at encapsulation often remain quiescent for an indefinite period. On the other hand, injury, weakened resistance, or possibly other causes sometimes lead to recrudescence of a previously inactive focus.

After the acute stage of osteomyelitis, whether circumscribed or diffused, and also, though less frequently, after the subacute or even the chronic form, partly localized and persistent subacute or chronic infective processes may remain. These are commonly manifested by the presence of sinuses communicating with the external surface, and from which pus is discharged; or, less frequently, as in diseases of the pelvic bones, with some hollow viscus, such as the bladder or rectum. Such sinuses are walled by granulation tissue, and usually communicate with some cavity in the bone or an area of suppuration involving its exterior.

Caries and Necrosis.—The term slough is usually applied to masses of dead tissue arising in the soft parts and undergoing separation from adjacent living structures. In osseous tissue the process by which the bone is destroyed—in other words, the alterations terminating in the death of a perceptible mass of bone—is called necrosis or death of the bone *en masse*. In the soft parts the lesion accompanying and following the separation of the slough, and limited to the adjacent living tissues, is called ulceration. In bone essentially the same process is termed caries.

Causes.—Death of the bone as a result of osteomyelitis has already been considered. Periosteal separation, embolism and thrombosis, and detachment of fragments of bone from the vascular structures from which they normally receive their nutrition may cause necrosis. The principal cause of necrosis is infection. This may assume the general characters already described when considering osteomyelitis, or may be a chronic infectious process, such as tuberculosis and actinomycosis, or, less frequently, such bacterial invasion of the bone as may arise from

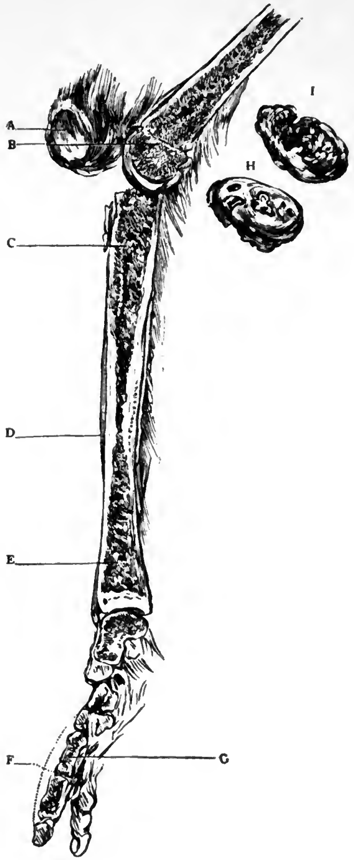


FIG. 398.—OSTEOMYELITIS INVOLVING THE TIBIA AND, TO A LIMITED EXTENT, THE LOWER END OF THE FEMUR. (The disease began at or near the epiphysis, and the case was reported under the title of acute infectious epiphysitis. The limb was amputated and the patient recovered. For detailed report see "Medical News," August 13, 1892.)

A. Patella turned backward and to one side, showing its lower surface. B. The lower extremity of the femur showing the line of the epiphysis and a distinct border of fatty degeneration just where the epiphysis joins the shaft. In the lower extremity of the femur are several small round or irregular dots marking the position of abscesses in the bone. The periosteum of the femur is slightly thickened just above the epiphyseal line. The epiphysis is normal, except that the cartilage covering it is superficially eroded. C, D, E. Sawed section of the tibia, showing the condition of its medullary canal; at the upper extremity of the tibia the shaft terminates in a jagged, irregular extremity that has been in apposition with the epiphysis. The epiphysis is placed over on one side at H, with a view of the upper surface, while at I the under surface is shown. Just above the line leading from C are two abscesses of considerable size; below this line, and extending to the line D, is to be noted the detachment of the periosteum. The periosteum is much thickened, the thickening fading off as the line E is approached. At C the bone-marrow was intensely red (hyperemic) and there were no less than a dozen small abscess cavities; the largest of these was not 0.5 cm. in diameter. The external compact portion of the bone is much thickened, and just opposite the leader from the letter there is considerable swelling along the line of the periosteum. The lower epiphysis of the tibia does not show to advantage; at the lower extremity of the shaft, near E, can be seen several small abscess cavities. The point G is the seat of the original injury. F marks the metatarsophalangeal articulation; a section of the metatarsal bone has been made and the upper fragment has been turned downward. The great toe is also shown. H is a view of the superior surface of the epiphysis of the tibia—the articular surface. It contained not less than five or six small openings that communicated with the abscess below and with the joint above. In some of them small fragments of necrotic bone are to be observed. The cartilaginous structures of the joint are also entirely destroyed, but the articular margins of the epiphysis show a slight fragment of the two semilunar cartilages. I is the same as H, except that it is a view of the inferior surface where it came in contact with the tibia. It will be observed that the epiphysis has been converted into an abscess cavity, the wall of which is formed by a hard cancellated layer of bone and by the articular disc. There was no periosteum continuous with the shaft and epiphysis, and hence the latter moved freely upon the end of the former, thus giving rise to the "flail joint" so characteristic of epiphyseal separation. The interior of the knee contained a considerable quantity of pus, and the synovial structures were also disorganized.

the metastases of the typhoid bacillus, colon bacillus, and influenza organism. (See Causes of Osteomyelitis, p. 811.)

Toxic Necrosis.—A form of necrosis observed in laborers in match factories is usually believed to be distinct from the other types of bone death, and is called phosphorous necrosis. It is not probable, however, that there is any material difference between this process and necroses arising from other causes. The phosphorus lessens the resisting power of the tissues, favors infection, and as opportunities for infection are

greatest in and around the teeth the inferior maxilla is most frequently involved. Caries (cavity formation in the teeth) seems to be almost a requisite, and is constantly present when the necrosis appears early.

Morbid Anatomy of Necrosis.—The masses of necrotic bone vary in size. The entire shaft of a long bone—as, for example, the humerus—sometimes exfoliates in one piece, or the epiphysis alone may be involved; not infrequently a fragment of one or both these structures is cast off. When considering gangrene (see p. 255), attention was called to the fact that the line of demarcation is an irregular zone, one side of which bounds the living tissues and the other the dead structures, and that the changes occurring within this area were those incident to the separation of the dead from the living structure, essentially a process of ulceration. This applies to the line of demarcation that would in time amputate a limb, as well as to the line of demarcation leading to the separation of a scarcely visible slough. Death of the bone and the process of separation from the viable tissue are comparable to the changes already noted as present in the soft parts. Where the dead tissue joins the living there appear accumulations of phagocytic cells which attack the osseous matrix, forming the line between the dead and living structures, and proceed with the separation of the necrotic mass. Many of these cells are clearly leukocytes belonging to the phagocytes already described. (See p. 98.) Other cells resemble the giant cells, and are probably identical with the myeloplaxes of osseous absorption, and in this locality are also called *osteoclasts*. Through the secretory and phagocytic action of the leukocytes and osteoclasts the dead bone is separated from the living, and constitutes the **sequestrum.** In the mean time suppurative processes may have communicated with the exterior and formed sinuses, through which, if the piece of dead bone be small, it may escape. Commonly, the surgeon assists nature by removal of the sequestrum. Occasionally, the dead mass is surrounded by fibrous or osseous tissue; in other words, a form of healing-in may occur.

If the infection is not arrested, destruction of tissue along the line of separation continues after exfoliation of the dead bone has taken place, and, as rapidly as granulation tissue is formed, it is liquefied by the contained bacteria and cells; and, in this way, the tendency toward repair is constantly opposed by the necrotic processes contingent upon the presence of microorganisms. This constitutes what is called caries or ulceration of bone. The character of the pus produced by such an infection depends largely upon the bacteria present. In some cases the pus is abundant, thin, and rich in pus-cells. This process is called **caries humida.** In other instances the amount of inflammatory exudate may be small and the discharge quite inconspicuous, to a certain extent justifying the name commonly applied—**caries sicca,** or **dry caries.**

Regeneration of Bone.—During or after the separation of the sequestrum, and as soon as the activity of the infection will permit, the adjacent osseous tissue begins repair by the production of new bone. The new bone is commonly evolved from the periosteum, and therefore forms around the sequestrum; the latter may be covered, except that here and there are small openings through which the pus escapes; the persistence of the suppuration is due to the continuance of a low order of infection, probably perpetuated by the irritation of the dead bone. The newly formed bone surrounding the sequestrum, is called the

involucrum. The dead bone acts as an irritant, and by its removal and the disinfection of the area involved, or sometimes as a result of victory of the phagocytes over the bacteria, repair proceeds by the production of new osseous tissue, which eventually replaces that destroyed by the processes of necrosis and caries. The newly formed bone is never uniform, smooth, and regular, like the normal, but uneven and clumsy, and but a crude reproduction of the destroyed tissue.

Chronic Nonsuppurative Inflammation of Bone.—In osteomyelitis, both acute and chronic, and in caries and necrosis the lesion is usually due to bacteria, the specific action of which is to induce suppuration or some necrotic and degenerative change, such as caseation. There can be no doubt that in bone a chronic productive process occurs which is comparable to interstitial fibroses observed in other organs. The difference, however, lies in the fact that the interstitial tissue of bone consists of a calcified matrix, while in other organs it is composed of a fibrillated structure. This particular type of inflammation is prone to occur in connection with syphilis, often when syphilitic processes are latent, and is frequently associated with the chronic productive periostitis already described. (See Fibrous Periostitis, p. 804.) It is present to a varying degree in the neighborhood of suppurative, necrotic, and infectious lesions involving the bone or paraosteal structures; it also develops around bone abscesses; in other words, **chronic productive osteitis** appears to result from the presence of irritants not of a kind or not sufficiently active to produce suppuration.

Morbid Anatomy.—The affected bone usually increases in size by apposition of new osseous or osteoid tissue from and under the periosteum. At the same time, in the long bones—as, for example, the femur—the marrow cavity is encroached upon and may be entirely replaced by new osseous tissue. (See Fig. 400.) The new tissue is commonly hard; the old bone also becomes dense. The density is sometimes sufficiently intense to preclude incision by a chisel or saw, and as such masses occur around sequestra, they frequently give rise to great difficulty during operations for the removal of dead bone. On account of the extreme induration of the bone the disease has received the name **osteosclerosis.** By reason of its apparent inflammatory origin it has been called **condensing osteitis.** (See Figs. 399 and 400.) In inflammations, attended by resorption of the osseous tissue surrounding the Haversian canals and the production of inflammatory elements in the Haversian lymph spaces, the bone is made abnormally porous and the condition is called **rarefying osteitis.** In bones so affected the marrow is abnormally soft and red, and unusually vascular.

Osteitis deformans[1] is a disease of unknown origin, usually occurring after middle life and manifested by great thickening of the skull and the long bones with marked softening and proportionately diminished resistance to pressure. The Haversian canals are enlarged, the contents cellular, and the new bone formed on the periphery of the old is also architecturally imperfect. Much of the new osseous growth remains uncalcified. The cranium is broadened, the femur is curved outward, and the tibia is arched anteriorly; the bones of the forearm bend toward

[1] Vincent, Thèse de Paris, 1904. Sonneberg, Inaug. Diss., Leipzig, 1904. Willard and Andrus, "Medicine," 1905, p. 59. Shattuck, "Boston Med. and Surg. Jour.," Jan. 12, 1905, p. 43.

the dorsal aspect, and the clavicles thicken and may be curved. In Sommer's case the ribs were widened. It is not universally agreed that

FIG. 399.—EXTERIOR OF FEMUR, SHOWING RESULT OF CHRONIC OSTEITIS ASSOCIATED WITH CHRONIC PRODUCTIVE PERIOSTITIS.

The growth of osteophytes over its surface is well exhibited. The bone also shows the usual deformity —great thickening, irregularity,—and presents the marked density with which these conditions are commonly associated.

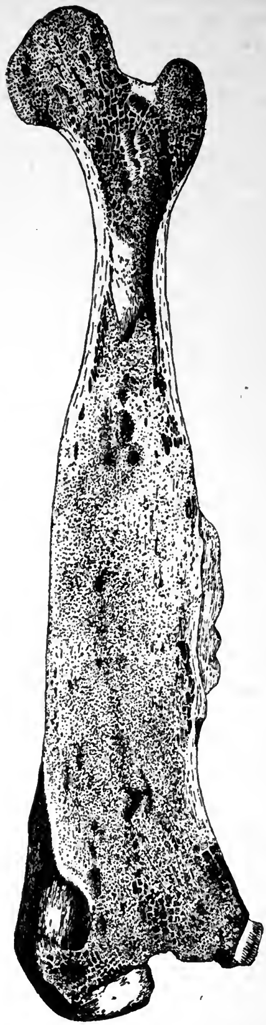


FIG. 400—FEMUR. LONGITUDINAL SECTION OF BONE SHOWN IN FIGURE 399.

It will be observed that the lesion is restricted to about two-thirds of the bone. The marrow cavity has been obliterated by the progressive osteosclerosis. The induration of the bone was such as to require the use of a lapidary's saw for making the section

the process is inflammatory; some believe that it is trophic; Fournier thinks it is a manifestation of syphilis.

FIG. 1.

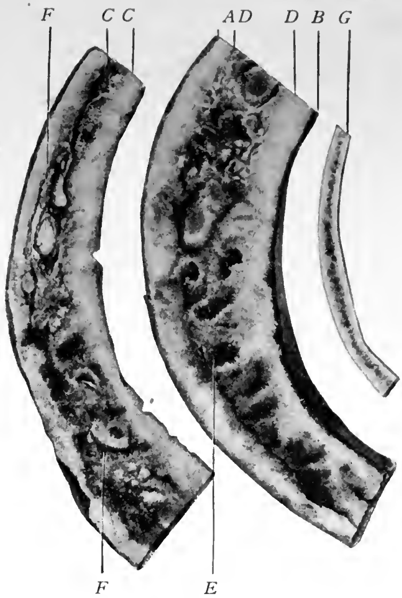


FIG. 3.

FIG. 2.

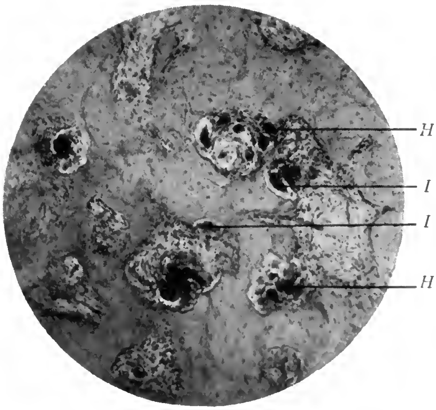


FIG. 4.

OSTEITIS DEFORMANS.

Case reported by Drs. Higbee and Ellis.

FIGS. 1 and 2. From photographs of patient.

FIG. 3, *A*. External table. *B*. Internal table. *C C*, *D D*. Mark the limits of the diploic area. *E*. Porous fibro-osteoid tissue. *FF*. Islands of calcified tissue. *G*. Section of normal skull for comparison.

FIG. 4, *H H*. Collections of giant cells in rather cellular masses of connective tissue. *I I*. Giant cells occupying lacunæ in the bordering osteoid tissue.

Tuberculosis[1] **of bone** may be manifested as an acute miliary process constituting a part of a general hematogenous (miliary) infection. In this form it is sometimes termed **acute tuberculous osteomyelitis.** The miliary tubercles disseminated through the bone-marrow histologically resemble the same process occurring elsewhere. The most frequent form of osseous tuberculosis is chronic in character, and is the commonest of all diseases of the bones. The lesion produced, commonly known as **chronic tuberculosis of bone,** may begin in the periosteum, bone-marrow, synarthrosis, epiphyseal disc, or epiphysis. The bacilli most frequently reach the bone through the circulation. Lexer, König, and others, have shown that tuberculosis of bone arises as a result of a tuberculous infarct, and Müller produced such a process by the intravascular injection of tubercle bacilli. Invasion may also occur from infection of contiguous structures, and possibly through the lymphatics. The lesion is most frequently located in or near the epiphyses, through involvement of which extension to the adjacent joint commonly occurs, constituting the usual source of tuberculous arthritis. As a result of proliferation of the fixed connective-tissue cells, as well as of leukocytic invasion, and more or less effort at peripheral vascularization, the formation of granulation tissue is brought about. Absorption of the adjacent bone progresses with advance of the tuberculous new-formation ; Rutizky, Ribbert, and others believe that osteoclasts are not necessary to the absorption of bone in the presence of granulation tissue. Certainly, along the lines of osseous invasion in tuberculosis there is evidence clearly indicating that decalcification and removal of the bone matrix without the presence of osteoclasts are in progress. In rare instances the process becomes quiescent, with condensation of the surrounding tissue, constituting a form of healing-in closely allied to that already described on page 151. Early in the process, as a result of the specific poison produced by the tubercle bacillus, marked changes occur in the newly formed vessels, followed by caseation beginning at or near the center of the diseased area. Such caseous areas increase in size by confluence of adjacent masses, extension into and absorption of the surrounding bone, and eventually, in many cases, perforation of the periosteum, and the induction of a **paraosteal tuberculosis,** thereby inducing what is often called a **cold abscess ;** the manifestation in this form is usually observed in connection with tuberculosis of the hip (**coxalgia**), knee (**tumor albus,** or **white swelling**), vertebræ (**Pott's disease**), etc. Necrosis of relatively large parts of the affected bone sometimes occurs. The necrotic mass most frequently, although not always, involves the whole or a part of the epiphysis. Destruction of the adjacent bone and invasion of the articular surface and joint are often observed, destroying the function of these structures. As a result of the destruction, erosion, or softening of the bone, distortion and deformity commonly occur. A notable example of deformity arising from this cause is seen in the spinal column, where softening of the bodies of the vertebræ gives rise to posterior arching or angular displacement (*kyphosis*). When the articular surface is reached, its destruction is almost inevitable, and, under the most favorable cir-

[1] Moret, Thèse de Paris, 1904. Lexer, "Arch. f. klin. Chir.," 1903, Bd. lxxi, H. 1. Hehle, "Wien. klin. Woch.," Sept. 22, 1904, p, 1011.

cumstances, there is probably nothing better to be expected than permanent ankylosis in the joint so affected.

Even in its most chronic form tuberculosis of bone presents at least two distinct dangers: (1) As in the septic osteomyelitis already described, general dissemination of the microbe may occur; in the former condition the result is septicemia or pyemia, and in the disease under consideration acute miliary tuberculosis is produced. In other cases the secondary manifestations may be restricted to the lungs. (2) Infection by pyogenic bacteria adds danger by augmenting the toxicity of the absorbed poison, or, rather, by adding new absorbable bodies, increasing the rapidity of the osseous destruction and rendering less efficient the protective and recuperative powers of the patient.

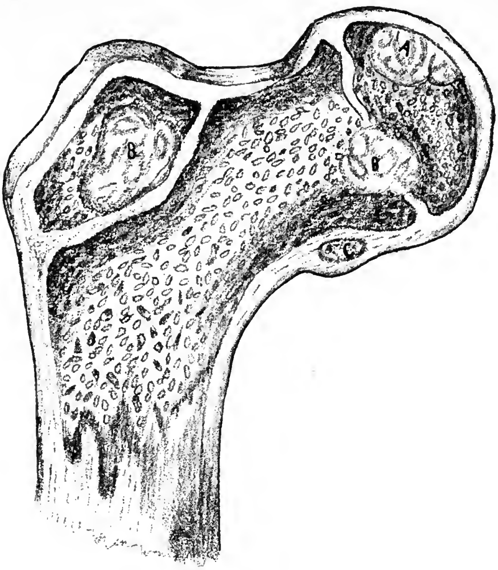


FIG. 401—FEMUR, HEAD AND NECK; BEGINNING TUBERCULOSIS. *A*. Small area of caseation in epiphysis just under articular cartilage, called subchondral. *B*, *B*. Same in epiphyses at point of junction with shaft; intraosseous. *C*. Subperiosteal. (After McArdle (redrawn) "Trans. Royal Acad. of Med. in Ireland," vol. vii, 1889, p. 140.)

Syphilis of bone, as in other tissues, induces a number of lesions, many of which are so dissimilar as to render it quite impossible to establish any characteristic relation between them. Some of the lesions of syphilis are probably due to lessened resistance on the part of the economy, giving rise to the occurrence of bacterial infections that of themselves induce changes in nowise syphilitic.

In *congenital syphilis* the bones at birth, or shortly afterward, show quite characteristic alterations at or near the epiphyseal line. Such changes are best exhibited in a longitudinal section of the lower end of the femur. The epiphyseal line is broadened and somewhat irregular, the irregularity being more marked on the articular side than toward its apophysis. Calcification in the neighboring areas is irregular, and proliferative changes in the adjacent bone and perichondrium (**syphilitic osteochondritis**) or periosteum occur, sometimes inducing a slight thickening, which, in advanced cases, may even resemble rickets. In other instances the irregular epiphyseal line assumes a grayish or bluish-white hue that, with the beginning of fatty changes becomes faintly yellow. Spontaneous separation of the epiphysis (**epiphyseolysis**) may occur, but is infrequent. The epiphysis is usually easily detached.

Histologically, irregular proliferation of the cartilage cells can be recognized, with an associated, unevenly distributed calcification, and, later, fatty degeneration in the newly formed elements. The prolifera-

tive changes in the periosteum and perichondrium, previously referred to, with the associated enlargement, have led some observers to regard such alterations as manifestations of associated syphilis and rickets, and may have been responsible for the belief that rickets is truly an evidence of syphilis—a view that has now been discarded.

Acquired syphilis induces no conspicuous bone lesion prior to the appearance of the tertiary stage. During the secondary stage there is probably some disturbance of the marrow, in common with the evident hyperplasia of other blood-making tissues, notably the lymph-nodes and spleen. In acquired syphilis, gummata develop most commonly in the periosteum; rarely as central lesions. Structurally, they do not differ from gummata occurring elsewhere. Degenerative and necrotic processes involving the gumma and extending to the overlying tissue may lead to external evacuation, followed by pyogenic infection. Rarely, pyogenic infection precedes the mucous or hyaline degenerative change observed in the syphiloma. Caseation sometimes occurs. Under appropriate treatment, and even without medication, more or less absorption may take place, which, associated with an osseous overgrowth, gives rise to osteophytic enlargement, irregularities of the surface, osteosclerosis, etc. (See Fibrous Periostitis, p. 804, and Chronic Osteitis, p. 815; also Figs. 399 and 400, p. 816.)

Actinomycosis of bone is rare in man; when present, the bones usually involved are the jaw, bodies of the vertebræ, ribs, or sternum. Occurring in the jaw, infection probably takes place through a tooth or tooth-socket. While the proliferative and necrotic changes of actinomycosis are in progress in the center of the bone, associated with resorption of the adjacent osseous tissue, subperiosteal apposition not infrequently occurs, thereby increasing the size of the bone. Suppuration, resulting from the activity of the fungus or from concurrent infection by pyogenic organisms, commonly occurs. The teeth loosen and often fall out. The tissue necrosis may extend through the oral mucosa; less frequently an external opening is formed. The discharge commonly contains the fungus, which can usually be demonstrated, except when late secondary or mixed infection produces such an excess of pus as to render the fungus difficult to find. (For Demonstration of the Fungus see page 167.) Encapsulation, similar to that observed in tuberculosis, is infrequent, and the disease rarely, if ever, assumes a quiescent stage.

Leprosy of the bone is manifested occasionally as distinct leprous nodules occurring in the medulla, and may closely resemble tuberculosis. Necrosis and more or less active inflammatory processes are occasionally present, particularly in the digits.

Glanders sometimes attacks a bone. Usually, it is the periosteum that suffers, except in the septicemic form of the disease, when micro-organismal invasion of the medulla may occur.

Fractures.—The term fracture is applied to solutions in the continuity of bone or cartilage. This definition includes separation of the epiphysis, which, surgically, is grouped with fractures.

Causes.—Certain factors are recognized as predisposing; for example, the position and function of bones as well as their shape and structure. Round bones are less liable to fracture than the long and flat bones, and the long bones of the extremities are more subject to injury, and hence are more frequently fractured, than the bones of the trunk.

Atrophic processes and diseases associated with rarefaction, increase the fragility, and hence favor the occurrence of fracture. The bones are also weakened by rickets; by cellular tumors that invade the marrow; by chronic infections, such as syphilis; by tuberculosis under certain circumstances; and by other diseases similarly influencing the density or chemistry of the bone.

The exciting cause is nearly always violence. This may be direct, as blows upon the bones, or indirect, as when the clavicle is fractured by a fall, the force having been transmitted to the injured bone through the bones of the arm and hand; in a similar way the base of the skull is sometimes fractured as a result of a fall, the individual landing upon the feet or in a sitting posture. Fractures resulting from muscular action are typified in the fracture of the patella occurring during the act of kicking. Fractures resulting directly from disease are sometimes spoken of as pathologic.

The *line of fracture* may be transverse, oblique, longitudinal, or spiral; it may be regular or irregular. It may traverse the bone in one direction, constituting a complete fracture, or it may be a fissure, not extending through. Bending, with fracture on one side (*greenstick fracture*), occurs in young bone. Detachment of bony prominences, such as the malleolus or trochanter, is sometimes observed. In the skull, fracture associated with inward displacement of a fragment is called a *depressed fracture*. When the bone at one point is broken into a number of fragments, the fracture is said to be *comminuted;* when broken in a number of places, or when a number of bones are broken, the fractures are said to be *multiple*. A fracture communicating with the external air through a wound in the skin or mucosa is said to be *compound*. Certain concurrent conditions constitute complications, and such fractures are spoken of as *complicated fractures*. Associated injury of nerves or vessels and extension of a fracture into the joint are examples of *immediate complications;* sepsis, faulty or imperfect union, and tumor formation at the point of fracture constitute remote or *secondary complications*.

As a rule, the fragments of the fractured bone do not immediately resume their normal relation one to another, and hence deformity occurs. One or both fragments may show longitudinal rotation (*rotary deformity*) in different directions or to different degrees in the same direction. Bending at the point of fracture (*angular deformity*) is frequently present. Lateral displacement, overlapping, and separation of the fragments are not infrequent. The rapidity and completeness of the reparative process are favored by an accurate coaptation of the fragments. That this, however, is not absolutely necessary is well known, aud is illustrated by figure 402.

Repair of Bone.[1]—Immediately following the injury an abundant extravasation of blood occurs; this collects around the fragments, between the ends of the compact portion of the bone, and invades, to a certain extent, the marrow. Following the hemorrhage the initial hyperemia of repair begins. This hyperemia is most marked in the periosteum and adjacent marrow, although all the surrounding tissues show it to a moderate degree. From the hyperemic areas leukocytic infiltration takes place—the leukocytes removing the cellular detritus

[1] Kraft, "Ziegler's Beitr.," vol. i, p. 85. Gröhé, "Arch. f. klin. Chir.," 1904, Bd. 72, H. 3. Matsuoka, "Virchow's Arch.," 1904, Bd. 175, p. 32.

resulting from the destruction of tissue and the disintegration of the extruded erythrocytes. Within from forty-eight—according to Kraft inside of forty-eight hours—to seventy-two hours after the injury proliferative changes take place in the connective-tissue cells, particularly those of the periosteum and the bone-marrow, although similar evidences of cell activity are to be recognized in the endothelium of the capillaries. This forms the germinal or reparative tissue, certain cells of which (*chrondroblasts*) arise from the genetic layer of the periosteum and from the medullary cavity and produce a matrix of temporary cartilage; from the same tissues are produced other cells, the function of which, later, is the completion of osseous formation; these are called *osteoblasts*. The mass of new tissue is known as chondroid or osteoid tissue, and constitutes what clinicians call *callus*. Structurally, the callus is more or less uniform, but its position has led to a description of three different parts: The external, circumferential, encircling, or ensheathing callus is that surrounding the bone; the internal, medullary,

FIG. 402.—FRACTURE OF THE FEMUR, SHOWING OVERLAPPING OF THE FRAGMENTS WITH ROTATORY DISPLACEMENT OF THE LOWER FRAGMENT, AND ATTEMPTED UNION IN THIS POSITION.

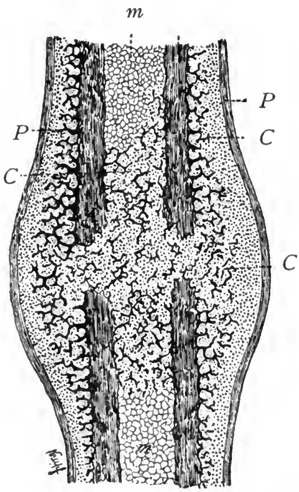


FIG. 403.—TEN-DAY-OLD FRACTURE.—(*Schmaus.*)
m, m. Bone-marrow. *P, P.* Partly detached periosteum. *C, C, C.* Deposit of osteoid and chondroid tissue under the periosteum and extending between the ends of the two fragments and into the medulla—the callus.

or pin callus occupies the central canal of the two fragments; while the callus between the compact portion of the two ends is called the intermediary or ring callus. The matrix produced by the chondroblasts is essentially a cartilaginous or chondroid tissue; it is at least a product of, if not a part of, their cytoplasm, and is shortly transformed into a marrow-like struc-

ture by the entrance of young blood-vessels. The latter are produced by budding projections from the nearest vascular twigs. (See Development of New Blood-vessels, p. 304.) The final step in bone production consists in calcification of the osteoid matrix. New marrow is formed by the projection of blood-vessels bringing with them a mantle of marrow-cells. From these, and possibly from the proliferation of adjacent cells with the abundant growth of new blood-vessels, the marrow cavity is reestablished.

Absorption of irregular and useless spicula begins early in the process, and is carried on by the leukocytes and osteoclasts already mentioned. After a time, varying in different cases, removal of the ensheathing or temporary callus takes place. This is accomplished through the intervention of the osteoclasts and chondroclasts, and requires, not uncommonly, many months for its completion. Wide separation of fragments, defective immobilization, the presence of muscle or other soft tissue between the fragments, and inherent deficient reparative power on the part of the tissues may prevent complete union.[1] The degree of faulty union varies. Sometimes after weeks there has been no perceptible effort at repair; in other cases fibrous tissue firmly joins the two ends, constituting *fibrous union*, which later, with rounding-off of the ends of the bone, terminates in the formation of a false joint (*pseudarthrosis*). Excessive callus-formation may lead to the coalescence of the reparative tissues arising from fractures of parallel bones at the same level, and, later, may firmly unite all the fragments constituting a synostosis.

Rickets[2]; Rachitis; Rachitismus; Morbus Anglicus.—Rickets is a disorder of nutrition in which the process of growth in the bones, muscles, mucous membranes, and many other tissues is profoundly influenced. The disease is not primarily one of bone. The changes seen in the bones are dependent upon defective nutrition during the period of most active osseous growth.

Etiology.—Rickets is a disease of childhood, usually developing toward the end of the first year, and nearly always before the end of the second or third year, although rare instances are reported in which the disease showed its first manifestations as late as the ninth year. Neither syphilis, unsanitary surroundings, disorders of the digestion, nor heredity are sufficient causes, although, with the exception of the last named, they may intensify the activity of the process. As the disease is not restricted to the human family, but also occurs in monkeys and in lions' whelps, certain experimental observations have been made. The experiments of Cheadle and Bland-Sutton seem to indicate that, at least in lions, the morbid condition may be avoided by the use of a diet rich in cream, proteids, and earthy phosphates. The necessity for fat in the diet seems to be thoroughly established, and the fact that children become rickety on a diet containing fat is presumed to depend upon the presence of associated digestive disturbances that prevent the emulsi-

[1] For recent studies on conditions causing non-union or malicious union, see Cornil and Coudray, "Revue de Chir.," July, 1904.

[2] Sinnhuber, "Zeit. f. klin. Med.," Bd. 54, Nos. 1 and 2. Spillman, "Arch. de Med. des Enfants," May, 1901. Edlessen, Kassowitz and others, "Centralbl. f. inn. Med.," Sept. 6, 1902. Pfaundler, "Jahrbuch. f. Kinderheilk.," 1904, Bd. 60. Nathan, "Med. News," Feb. 20, 1904, p. 391. Freeman, "Arch. of Pediatrics," April, 1904.

fication and consequent absorption of this body; therefore changes in the diet after the occurrence of catarrhal processes in the alimentary canal often fail to modify the disease. The beliefs that it is an infection (Edlessen), an intoxication (Kassowitz), and that it depends upon disease of the thymus (Mendel) rest upon evidence which is not conclusive. There is a general conviction that it depends upon dietetic errors or digestive disturbances, but exactly how these factors operate remains undetermined.

Morbid Anatomy.—A conspicuous and usual change is the development of the *rachitic rosary*, which consists of an enlargement appearing at the junction of the ribs and costal cartilages, usually more marked on the inner than on the external surface, and commonly conspicuous at the junction of the fifth and sixth ribs with their respective cartilages. This enlargement has been recognized in the fetal skeleton, and is sometimes present at birth. The *craniotabes* of Elsasser consists of absorption and thinning of the cranial bones, most marked in the parietal and occipital regions. The marginal membranous portions of the bone do not show the normal progressive ossification. Associated with the absorption of the inner table and the thinning, there also occur hyperplastic changes, swellings, or bosses over the frontal, parietal, or occipital bones. The sutures, excepting the mediofrontal, show delayed union, and the anterior fontanel often remains open until the end of the second year or even later. The teeth appear late and frequently not in their proper order; they become carious early. In addition to the rachitic rosary, already mentioned, the chest shows flattening on the sides, and the sternum is thrust forward (*pigeon-breast*). Posterior and lateral curvature of the spine occur. The iliac crest is sometimes thickened and the pubic arch may be narrowed. Juxta-epiphyseal enlargements similar to those observed on the ribs, appear in the long bones, particularly the radius, ulna, tibia, and femur. The periosteum seems more vascular than normal, and strips off with unusual readiness. The underlying bone is commonly soft, and frequently bends; green-stick fractures may occur.

Histologically, there is evidence of "excessive preparation for bone formation which does not occur" (Jenner). Osteoporosis, depending upon lacunar absorption, is present. Unusual periosteal production of osteoid tissue gives rise to osteophytes that, with the advent of recovery, are converted into bone, thus perpetuating the deformity produced by their growth. The line of calcification in the juxta-epiphyseal cartilage is irregular, poorly marked, or may be absent. There is an abundant production of osteoid matrix, into which medullary vessels are projected without the usual accompanying deposit of bone.

In addition to the osseous changes already mentioned, the ligaments of the joints are lax and frequently give way. The muscles usually show deficient and imperfect striation, and during life are weak. The liver and spleen are not infrequently enlarged, and commonly show increase in fibrous tissue. More or less evidence of associated catarrhal inflammation of the mucosæ is usually present.

Tumors of Bone.—Primary epithelial neoplasms do not occur in normal bone; the complex developmental processes occurring in the maxillæ are sometimes attended by the presence of epithelial vestiges from which carcinoma occasionally arises. Secondary cancer of the

bones may be due to direct extension or to lymphatic involvement of osseous tissues within the lymph area draining a primary cancerous focus. Herbert Snow has particularly investigated this question, and, although his views have been criticized, appears to have demonstrated that cancerous foci may lie dormant in the bone-marrow for months. When active, they give rise to rapid absorption of bone, softening, and frequently fractures. Metastasis of thyroid tissue to bones is mentioned on page 784. Myxoma of bone is rare; Soubeyran[1] has been able to collect six cases of pure myxoma; most tumors of this nature are myxosarcomata. Katholitzky has recorded an instance of lymphangiomatous involvement of bone. Angiomata of bone have been described, and extremely vascular masses called bone aneurysms sometimes occur; Gaylord[2] has collated the reported cases of the latter group and records an original observation; he believes such masses are usually sarcomatous. Chondromata are not infrequent tumors of bone; they develop from the periosteum or the epiphyseal junctions and are generally believed to arise from vestiges of embryonal cartilage; in some cases they are multiple. Sarcoma originates in the periosteum or in the interior of the bone; any type of cell may be present; giant-cell sarcomata frequently involve the maxillæ and are the least malignant. Occasionally sarcoma of bones is congenital; tumors of this type may begin in the medulla and cause extensive osseous resorption terminating in fracture without manifesting any external evidences of their presence; they sometimes follow injury. An important but rather infrequent tumor of bone is one arising in the marrow, apparently belonging with the sarcomata, and known as the **myeloma**[3]; the condition is also called **myelomatosis** and Kahler's disease. The affection during life is often diagnosed osteomalacia. In one type of the morbid process the bone alone is involved, and in another metastases to the lymph-nodes and other structures occur. When the bodies of the vertebræ are involved, kyphosis results. The cells composing the tumor are round or polyhe-

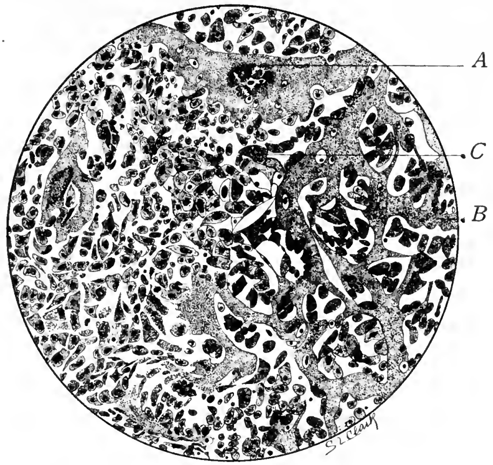


FIG. 404.—SARCOMA, MIXED-CELL, WITH CALCIFICATION OF PART OF THE INTERCELLULAR MATRIX; OSTEOSARCOMA.
A. Calcified area in osteoid matrix. *B*. Osteoid tissue which, in some areas, gives rise to an alveolar arrangement. *C*. Osteoblastic cell.

[1] "Revue de Chir.," April 10, 1904, p. 589.
[2] "Annals of Surgery," June, 1903, p. 834.
[3] Vignard and Gallavardin, "Revue de Chir.," Jan. 10, 1903. Weber, Hutchison and Macleod, "Amer. Jour. of Med. Sci.," Oct., 1903. Lindemann, "Deut. Arch f. klin. Med.," 1904, Bd. 81. Meltzer, "Med. Record," June 18, 1904, p. 989. Jellinek, "Virchow's Arch.," 1904, Bd. 177, p. 96.

dral, and resemble the plasma cell (p. 303). Usually the growth develops primarily in the marrow of the vertebræ, ribs, and sternum, but eventually affects the marrow of all the bones. The affection is also characterized by the presence in the urine of a peculiar proteid called Bence-Jones albumin.

Cysts of bone[1] may result from necrotic and liquefactive changes in tumors (p. 371), occasionally develop from embryonal vestiges (dentigerous cysts), and are sometimes due to parasites (hydatid). The osseous system is rarely the seat of dermoid cysts.

THE JOINTS.

A **joint** is composed of the articular ends of two or more bones; of the capsule, ligaments, or other structures binding the bones together and retaining them in their proper relations one to the other; and of the synovial membrane, the function of which is to lubricate the articulating surfaces. The ends of the bones entering into the articulation are commonly covered by articular cartilages, and may be further protected by intermediary structures not properly belonging to either bone. The capsule and ligaments are composed of fibrous tissue more or less rich in elastic elements, dense and firm, offering certain protection to the joint and resisting intra-articular accumulations. The synovial or serous membrane of the joint possesses an outer layer of elastic fibers and fibrillar tissue, continuous with that of the adjacent structures, and an exposed stratum of flattened endothelial cells.

Malpositions and malformations of the joints may be congenital or acquired. The congenital malformations are usually dependent upon developmental arrest, or abnormal pressure involving particularly the articular surfaces, and are manifested by such deformities as club-foot, knock-knee, club-hand, etc. The acquired malpositions and malformations are either the result of disease that more or less profoundly alters the bone, or of trauma, relaxation of the ligaments, or unusual or abnormal muscular contraction or other applied force leading to altered relations between the articular surfaces and constituting a lesion called a **luxation,** or dislocation.

Fatty, hyaline, and **mucoid degenerations** occur in the synovial membrane, and occasionally in the articular cartilage. The hyaline material may resemble lardacein, even to the extent of yielding the appropriate reactions. Fat accumulates in the synovial fringes, and later the same may be converted into cartilage or chondroid substance.

Metaplasia of the cartilage into fibrous, mucoid, or osteoid tissue occasionally occurs, and in rare instances it may be, in part at least, converted into a marrow-like substance.

Infiltrations into Joint Structures.—*Calcareous infiltration* not infrequently follows reparative processes in the neighborhood of a joint and inflammations of the joint capsule and synovial membrane, particularly when chronic, and also occurs as a result of chronic infection, notably tuberculosis, either of the joint or of an adjacent structure. The condition is sometimes noted in old age independent of evident gross lesions of inflammation.

[1] Turner, "Edinburgh Med. Jour.," Nov., 1903. Beck, "Arch. f. klin. Chir.," 1903, Bd. lxx, H. 4. Bloodgood, "Jour. Amer. Med. Assoc.," Oct. 15, 1904, p. 1124.

Hemorrhage into the joint (**hemarthron**) or into any structure of the joint is frequently associated with the presence of pigment held in the matrix of the cartilage and fibrous tissue as well as in the capsule of the normal cartilage cell. I have discussed the **hemarthrosis of hemophilia** on page 263. Reference has been made to the uratic deposits occurring in the cartilages in gout. (See p. 238.)

Loose Bodies in the Joints.—These are occasionally seen in the joints of the elbow, wrist, hip, shoulder, and ankle, but in from eighty-five to ninety per cent. of the cases the knee-joint is affected. Their presence in arthritis deformans will be referred to when discussing that affection. They may result from detachment of the articular cartilage, or may consist of a fragment of bone or synovial fringe that has become cartilaginous, fibrous, or lipomatous, or they may be produced by the exfoliation of fibrinous, calcareous, or inflammatory masses. Loose bodies are usually small and irregular, rarely attaining the size of two or three centimeters. They are sometimes multiple; Thomson[1] removed a pint of loose bodies from the knee-joint. The structure is largely dependent on the origin, as indicated by the foregoing list of causes. Occasionally, a loose body may be attached.

Inflammations of Joints.[2]—Theoretically, it is possible for an inflammatory process to be restricted to any one of the tissues entering into the formation of the joint, or it may involve a number or all of the articular structures. Inflammation of the cartilage is called **articular chondritis**; inflammation of the synovial membrane, **synovitis**; inflammation of the joint capsule and ligaments, **parasynovitis**; while inflammatory processes involving all these structures are grouped under the name of **panarthritis.** Chronic inflammatory processes or inflammations of a low grade may be restricted to one of the foregoing structures, but joint inflammations are rarely simple processes, and usually include more or less involvement of all the structures.

Inflammation is sometimes restricted to a single joint (*monarticular arthritis*, *monarthritis*), or a number of joints may be simultaneously affected, or in quick succession (*polyarticular arthritis*, or *polyarthritis*).

Acute simple serous synovitis is an inflammatory process not due to pus-producing organisms, or at least to pyogenic bacteria of such virulence as to lead to the accumulation of polymorphonuclear leukocytes (pus); whatever the cause may be, it gives rise to a more or less abundant serous or synovial accumulation in the joint cavity or adjacent bursæ, or both.

Etiology.—Such injuries as contusion, sprain, pinching of the synovial folds, loosening of articular cartilages, and loose bodies in the joints may be taken as types of the purely local causes. A similar, although possibly not identical, inflammatory process is induced by the presence in the circulation of irritants, either bacterial or chemic or possibly both. The joint inflammation of acute rheumatism[3] partakes of many of the characters of an acute serous synovitis, and is clearly an infection (p. 112). The inflammatory process in gonorrhea is usually associated with

[1] "Lancet," March 16, 1901.

[2] Guyot, "L'Arthritis Maladie generale, Microbienne et Transmissible," 2e ed., Paris, 1905.

[3] Walker and Ryffel, "Brit. Med. Jour.," Sept. 19, 1903, p. 659. Poynton, "Brit. Med. Jour.," May 14, 1904; also "Practitioner," June, 1904, p. 864.

characters of an acute serous synovitis, and is clearly an infection (p. 107). The gonococcus commonly causes an abundant migration and accumulation of polymorphonuclear leukocytes, and hence justly the process should be considered with the suppurative form of arthritis, although cases essentially serous in nature do occur.

Morbid Anatomy.—The process may be monarticular or polyarticular. It is most frequent in the large joints possessing complicated internal structures, and particularly those subjected to the greatest strain and most liable to injury. Such joints are those of the knee, ankle, elbow, and wrist. The initial manifestations are usually in the synovial membrane. There is probably at first a scantiness in the synovial secretion, associated with hyperemia of the membrane, the bright red surface of which contrasts strongly with the pearly-white articular cartilages. The first fluid extruded is usually quite clear, but later is cloudy from the addition of migrated leukocytes and desquamated endothelial cells. Erythrocytes are occasionally present, particularly in the earlier stages. The synovial inflammation partakes of all the characters and variations occurring in inflammation of serous membranes, and hence may be serous, dry, fibrinous, or serofibrinous. (See Inflammation of the Serous Membranes, p. 461.) The amount of fibrin varies; occasionally, the disease runs its course without the presence of fibrin in the fluid evacuated by operation. On the other hand, extensive fibrinous deposits sometimes occur, and these, going on to organization, form adhesions, thicken the synovial membrane, and, with added connective-tissue elements in the capsule and lessened secretion, terminate in a form of fibrous ankylosis. Ankylosis is more likely to occur in the dry or fibrinous type of this disease. Occasionally, a serous accumulation persists for a long time in the joint, constituting a form of effusion called **hydrops arthrosis.** In the dry form, and occasionally in the serous form, when associated with fibrinous deposits, loose masses of fibrin are found; sometimes these are attached to the long, thread-like fimbriæ of the synovial membrane. Under more favorable conditions the serum is often absorbed, the fibrin, if small in amount, liquefies and is removed by the vessels and lymphatics, and the joint returns to the normal; subsequently, such joints usually possess a rather high degree of susceptibility to irritation.

Acute Suppurative or Purulent Arthritis.[1]—As elsewhere, suppuration within a joint can be produced by the injection of purely chemic bodies; that it is ever engendered in this way, except experimentally, does not seem probable. Infection by any of the pyogenic bacteria may give rise to a suppurative arthritis; as causes, the pyococci should be first mentioned; the gonococcus, pneumococcus, Bacillus coli communis, typhoid bacillus, and occasionally other organisms, may induce a purulent arthritis. The infection sometimes reaches the joint through a wound communicating with the surface. In other cases a peri-articular suppurative process involves the articular structures. Occasionally, suppurative foci in or near the articular end of the bone penetrate the joint. (See Fig. 398, p. 813.) In other cases the joint is infected through the blood; as examples of hematogenous infection may be cited suppurative forms of gonorrheal rheumatism, and the joint

[1] Marsh, "Brit. Med. Jour.," Dec. 13, 1902, p. 1831. von Bruns, "Berl. klin Woch.," July 4, 1904. Tashiro. "Ziegler's Beitr.," 1903, Bd. 34, p. 540.

complications of pneumonia, septicemia, pyemia, typhoid and puerperal sepsis.

Morbid Anatomy.—Like the acute simple form, the disease may be monarticular or polyarticular. While it is not improbable that the affection begins as a synovitis, in a large number of cases it quickly becomes a panarthritis. The initial stage of the process closely resembles that observed in the acute serous synovitis. The hyperemia is usually more marked and the leukocytic migration far in excess of that usually seen in the synovial inflammation described. In the latter condition the hyaline cell is usually most abundant, while in the suppurative form the polymorphonuclear is the predominating leukocyte. The distention of the joint may be marked. Erosions in the cartilage occur, sometimes associated with exfoliations (necrosis) of considerable size. Occasionally, the whole epiphysis may be detached, particularly when the original focus was in the bone. Necrotic spots appear in the joint capsule; these, when extensive, lead to its disintegration, withdrawing the normal support of the joint and permitting luxation (*pathologic luxation*); later, peri-articular suppuration is induced, which often involves the adjacent tendons, tendon-sheaths, and bursæ, burrowing along the course of such structures or presenting at the surface as a peri-articular abscess. The extent of damage to the joint is largely dependent upon the activity of the process, but more particularly upon the length of time it is allowed to progress without evacuation of the inflammatory accumulation. The early withdrawal of the infection favors the progress of repair; if, however, it be permitted to persist, erosion of the articular ends of the bone occurs, with the destruction of the synovial membrane and joint capsule, leaving little better to be hoped for than a more or less firm fibrous ankylosis in which extensive calcareous infiltration takes place, resulting in what is practically a bony ankylosis.

Gouty Arthritis.[1]—The articular inflammation occurring in gout is in part a serous synovitis associated with the precipitation of sodium biurate upon and in the articular cartilages, and also, although not to the same extent, in the joint capsule and ligaments and synovial membrane, and occasionally in the peri-articular structures as well. Late in the process the peri-articular deposit is constant. The acicular crystals are deposited in the cartilaginous matrix and in the capsules of the cartilage cells, as well as upon the free surface. The cartilage near and upon the adjacent bone usually escapes. The deposit may occur in normal cartilage, and the late degenerative processes, terminating in erosion, exfoliation, or necrosis, are truly secondary to the irritation of the urate present. From the experiments of Garrod and from other studies it would appear that the uratic infiltration comes from the synovia rather than from the osseous or cartilaginous tissues themselves.

That the synovial membrane is not the tissue essentially at fault is shown by the fact that deposits also occur in the eyelid, ear, and nose. The clinical notes justify the belief that the deposits occur only before and during a paroxysm. Associated with the infiltration by the biurate, or probably secondary to the necrosis that accompanies it, deposition

[1] Symposium on Gout, "Practitioner," July, 1903, pp. 1 to 106 Futcher, "Jour. Amer. Med. Assoc.," Nov. 26, 1904, p. 1507. Rosenbach, "Virchow's Arch.," 1905, Bd. 179, p. 359.

of calcium carbonate and phosphate also takes place. These sometimes induce peri-articular enlargement, constituting the so-called *tophi.* The gouty inflammation is most frequent in the metatarsophalangeal joint of the great toe. When the deposit reaches the surface, infection followed by suppuration occasionally ensues. The discharge commonly contains the needle-like crystals of sodium biurate. (See Uric Acid Deposits, p. 238.)

Osteoarthritis[1]; *chronic arthritis; arthritis deformans; rheumatoid arthritis; dry arthritis; trophic arthritis; spondylitis deformans* (vertebræ), are all synonyms indicating the protean manifestations of the disease, or expressions of the various views that have been held as to its cause. The etiology of the affection remains undetermined; it has been suggested that it is (1) primarily a disease of the nervous system, (2) an infection. Those who incline toward the bacterial origin of deforming arthritis are undecided as to whether it is a specific infection—due to a single organism—or can be produced by any one of a number of bacteria. The suggestion has been made that it is an intoxication; this view, however, has not been regarded with favor. Osteoarthritis may be monarticular or polyarticular, and may, in certain stages of its evolution, resemble acute rheumatism and gout. In the monarticular form the hip, knee, shoulder, and elbow most frequently suffer. The polyarticular manifestation is a disease of the smaller joints of the extremities and of the vertebræ (**spondylitis deformans**). The inception of the disease frequently occurs early in adult life, and is usually preceded by trauma, sometimes by rheumatism. It is a panarthritis, usually beginning in the synovial membrane or in articular cartilages by proliferation of the cartilage cells and, later, leading to the formation of a superficial fibrillated matrix; as the fibrillation is particularly marked on the surface, the cartilage is thereby given a velvety aspect. Absorption, necrosis, and exfoliation of the proliferated cartilage appear later. From the margin of the cartilage the process extends to the synovial membrane—if this structure has not been attacked earlier—the connective tissue of which becomes cellular and elaborates a chondroid or osteoid matrix, in which calcific deposits form. The villi of the synovial membrane become exuberant, and not uncommonly loaded with fat, constituting the so-called **aborescent lipoma.** As a result of myelogenous absorption and lacunar atrophy, the density of the articular end of the bone is lessened, and, later, gelatinoid or mucoid areas develop in its interior. Excavations occur on the articular surface that, with lateral extensions from the periphery of the articular cartilages, entirely destroy the architecture of the joint. Osteophytic growth from the bottom of the acetabulum, with lateral extensions from the head of the femur, entirely change the character of the joint, the acetabulum becoming the ball and the femur forming the socket. Such alteration in the joint

[1] Schüller, "Berl. klin. Woch.," 1900, Nos. 5, 6, 7. Curcio, "Gazz. degli Ospedali e delle Clin.," Oct. 30, 1904. Ruhräh, "Amer. Jour. of Med. Sci.," Nov., 1903. Edsall and Lavenson, "Amer. Jour. of Med. Sci.," Dec., 1903, p. 991. McCrae, "Jour. Amer. Med. Assoc.," Oct. 8, 1904, p. 1027. Bannatyne, "Rheumatoid Arthritis: Its Pathology, Morbid Anatomy, and Treatment," 3e ed., 1904, London. Goldthwait, "Boston Med. and Surg. Jour.," Nov. 17, 1904. Richardson, "Boston Med. and Surg. Jour.," March 9, 1905, p. 263; see also a number of papers on Chronic Joint Disease in same journal, Nov. 17, 1904. McCarthy, "N. Y. Med. Jour.," April 8, 1905, p. 681.

is not at all characteristic or constant, but is mentioned as illustrating the remarkable deformity with which the process may be associated. Detachment of portions of osteophytic growth and loose cartilages with separation of the enlarged fimbriæ give rise to loose bodies in the joint. The extensive production of osteophytes and fibrous tissue usually gives rise to fixation or even to ankylosis, while the osseous resorption favors the occurrence of luxation or weakens the bone in the neighborhood of the joint, permitting fracture. Atrophy of muscles and wasting of adjacent structures make more evident the articular deformity.

Neuropathic Diseases of Joints.[1]—*Spinal* and *neurogenous arthropathies* are forms of joint-change commonly associated with locomotor ataxia, with syringomyelia, and less frequently with compression, concussion, and other lesions of the spinal cord, including degenerative change in the anterior horns. The disease is monarticular in about eighty per cent. of the cases, and usually involves the larger joints,—namely, the knee, hip, shoulder, or elbow,—although it is occasionally seen in the smaller articulations of the hand and foot, and very exceptionally in the spine. In some cases osteophytic growths occur, usually beginning in the cartilage and cellular elements of the capsule and periarticular tissues. This constitutes the so-called hypertrophic form. In the atrophic form degeneration and absorption of the articular surface and part of the adjacent bone occur, with relaxation of the ligaments, permitting or favoring luxation. The head of the bone—as, for example, the femur—may be completely absorbed. Serous effusion into the joint is not infrequently present; except in the earlier stages, it is rarely marked. The disease was studied by Charcot, and is frequently spoken of as *Charcot's disease of the joints*. The investigations of Wilde indicate that the joint lesion starts from an injury; changes in the sensory nerves render the patient less susceptible to pain, the absence of which causes neglect and perpetuates the alterations in the articular structures and contiguous bones.

Tuberculosis of joints, also called articular tuberculosis, tumor albus, white swelling, scrofulous or strumous joint disease, fungous disease of the joint, caseous arthritis, tuberculous abscess of the joint, cold abscess of the joint, and by other names indicating either the etiology or anatomic changes, results from infection of one or more of the articular structures by the tubercle bacillus. The condition is most frequent in children—over eighty per cent. of the cases occurring before the fifteenth year. The disease commonly attacks the hip, knee, or ankle, although the shoulder, wrist, and elbow occasionally suffer; a process practically identical, affecting the vertebræ, is called *Pott's disease of the spine*. The disease is nearly always monarticular; to this, however, there are occasional exceptions. A history of trauma is frequently present; the injury may induce an inflammation that later becomes infected by the tubercle bacillus; it is also probable, however, that trauma[2] acts by irritating or breaking open a latent or quiescent area of tuberculosis in the adjacent bone. It is usually held that the tubercle bacilli reach the area involved through the circulation, coming from a primary lesion

[1] Wilde, "Deut. Zeit. f. Chir.," Oct., 1902, Bd. 65. Bressaud, "Arch. Gen. de Méd.," 1903, No. 52. Kollarits, "Neuro. Centralbl.," April 1, 1904, p. 304. Frank, "Centralbl. f. d. Grenzgebiet. der Med. u. Chir.," Bd. vii. No. 17, 1904.

[2] Petrov, "Zentralbl. f. Chir.," Nov. 26, 1904.

elsewhere, as, *e. g.*, a latent tuberculosis of the bronchial glands, or possibly mesenteric lymph-nodes. As already indicated (p. 817), the initial lesion of the process is usually in the adjacent epiphysis, from which it extends to the involved joint, constituting the so-called *osteopathic* variety of the disease. In other cases the disease appears to arise in the synovial membrane; in other words, it is a primary involvement of the joint, and is called *arthropathic*.

Morbid Anatomy.—Recent studies seem to indicate that we are justified in recognizing at least two forms of articular tuberculosis; one is the old familiar type attended by extensive caseation and osseous absorption, and properly called caseous tuberculosis. In the second variety cheesy masses are not produced, although hyperplasia of the synovial membranes and fibrous ankylosis frequently occur; this type may be called chronic fibrous or ankylosing arthritis.

Chronic Caseous Tuberculosis of Joints.—Whether involving the joint from adjacent bones or beginning as a chronic synovitis, the process rapidly becomes a panarthritis. The disease is occasionally preceded by a stage of hydrops arthrosis. The abundant production of granulation tissue occurs not only from the synovial membrane, but the fungoid mass may be projected from the tuberculous bone, thus filling the joint with granulation tissue containing, in its earlier progress, numerous tubercles in various stages of evolution. In this tuberculous tissue caseation rapidly ensues, distending the joint by accumulated caseous detritus. The joint capsule is more or less rapidly invaded; and further extension of the process, along the line of least resistance, frequently occurs. Like other forms of tuberculosis, the lesion is sometimes arrested, and healing-in may occur at any stage of its evolution. In the majority of cases, however, destruction of the joint takes place. The articular extremity is usually riddled by perforations from which the granulation tissue projects, or such openings communicate with the caseous areas in the adjacent zone. Epiphyseal separation is sometimes observed. With healing-in, extensive calcareous infiltration takes place, terminating in permanent ankylosis.

The dangers of this form of tuberculous arthritis are twofold. In the first place, the local lesion, as a result of the hematogenous dissemination of the tubercle bacillus, may give rise to general miliary tuberculosis. Extensions along the bone sometimes lead to tuberculous osteomyelitis, caries, and necrosis; and disastrous complications follow infection by pyogenic organisms. The weak protective powers present in the diseased tissues favor inoculation by pyogenic bacteria, and in this way there is added to the local tuberculosis one or more of the dangers incident to acute suppurative osteomyelitis.

Chronic fibrous tuberculous arthritis[1] is more likely to affect a number of joints simultaneously or in succession than the typical caseous form. In this type of the affection the lesion resembles the chronic hyperplastic tuberculosis of other tissues (p. 153), and in some cases possesses the clinical characters of arthritis deformans. Caseation is inconspicuous or absent, the articular and para-articular fibrous tissues are thickened, serous exudates into the joint occur, and connective-tissue metaplasia

[1] Edsall and Lavenson, "Amer. Jour of Med. Sci.," Dec., 1903. Levison, "Jour. Amer. Med. Assoc.," Jan. 23, 1904. Poncet and Leriche, "Rev. de Chir.," Jan. 10, 1905, p. 1.

of the cartilage, and subsequent cicatrization, terminate in ankylosis. The danger of systemic infection is much less than in the caseous form of the affection; it is probable that many cases of fibrous joint tuberculosis are mistaken for chronic rheumatism, arthritis deformans, and other affections, some of which are clearly non-tuberculous.

Syphilis of the joints[1] occurs in both the inherited and acquired forms of the affection. It may be manifested by a hydrops arthrosis, chronic serous synovitis with the accumulation of considerable fluid in the joints, or a chronic fibrous ankylosing inflammation with connective-tissue metaplasia of the articular cartilages. Fournier has described a deforming type of syphilitic arthritis resembling arthritis deformans. Gummata sometimes develop in the synovial membrane (gummatous synovitis), or, extending from the epiphysis, may involve the articular cartilage; in either of these forms the resemblance to tuberculosis is clinically sufficiently marked to justify the term pseudo-white-swelling sometimes given to the affection. Syphilitic inflammation of the joints is often a polyarthritis.

Ankylosis is the name given to that condition in which a joint becomes useless by reason of fixation. The name literally indicates angular deformity, which may or may not be present. When the fixation is dependent upon lesions around the joint, upon fibrous changes in the joint capsule, or upon muscular contraction and similar conditions, it is said to be a *false* or *pseudo-ankylosis*. On the other hand, when the fixation arises as a result of structural changes in the articular surfaces, leading to osseous or calcific union between the bones entering into the joint, the condition is called *true ankylosis*. Such ankylosis commonly follows protracted inflammatory processes affecting the joint, suppurative arthritis, tuberculosis, and similar inflammatory or necrotic processes.

Morbid Anatomy.—The alterations observed in the joint depend largely upon the cause. Theoretically, in false ankylosis the articular surfaces are normal. There is usually considerable increase in the fibrous tissue of the capsule, which may be also calcareous. Further, the capsule adapts itself to its long-continued quiescent position, and, with the removal of the cause, if such be possible, considerable time is necessary for the reestablishment of pliability and elasticity in the altered ligaments. In true or osseous ankylosis the formation of new bone or extensive calcific deposits in granulation tissue, gives rise to fixation. Fractures involving joints may, in the process of uniting, permanently fix the articular surfaces. Extensive calcareous infiltration of inflammatory products and inefficient attempt at osseous repair may entirely destroy the articular structures.

[1] Morestin, "Arch. Gen. de Méd.," 1901, vol. 5. Hippel, "Münch. med. Woch.," Aug. 4, 1903, p. 1321; also Jordon, same journal, p. 1324. Paton, "Brit. Med. Jour.," Nov. 28, 1903, p. 1389. Fletcher, "Lancet," Nov. 19, 1904. Dunlop, "Edinburgh Med. Jour.," Dec., 1904.

CHAPTER XVI.

THE NERVOUS SYSTEM.[1]

General Considerations.—*Anatomy and Histology.*—It is not within the province of this book to discuss in a detailed or minute manner the anatomy of the nervous system, and those who desire such knowledge are referred to anatomies and special text-books on the subject.

The nervous system is composed of (1) the *brain* and *spinal cord*, which together constitute the *central nervous system*, and (2) the *peripheral nervous system*, consisting of multitudes of nerve-fibers that are projected in small bundles, known as *nerves*, from both the brain and cord to the various parts of the body; in addition to the foregoing, there is what is known as (3) the *sympathetic nervous system*, which, although probably developed independently, is to be regarded as having a direct relation with the cerebrospinal system.

The brain and cord are covered by three connective-tissue investing membranes, collectively known as the *meninges;* these are in intimate relation with the structures that they inclose, and are to a certain extent influenced by many of the diseases of the brain and cord, which structures are also affected in a number of lesions beginning in the overlying membranes.

The covering directly in contact with the surfaces of the brain and cord is called the *pia mater;* next to this is a layer of extremely delicate tissue directly continuous with the foregoing, and, therefore, to be regarded as really a part of it, known as the *arachnoid*, the two structures constituting the pia-arachnoid; and, finally, covering the inner surface of the skull and lining the bony wall of the spinal canal is a very dense, comparatively thick membrane, which has received the name *dura mater.* The membranes around the cord are continuous with those covering the brain, of which they are merely prolongations; these membranes, though becoming much thinner, and in part losing their identity, are further projected as coverings of the nerves passing from the brain and cord; the dura becomes the *epineurium;* the arachnoid, the *perineurium;* and the pia, the *endoneurium.* Although it should be clearly understood that the several membranes constituting the meninges are respectively the same in both the brain and cord, it is equally important to know that they differ from one another in several minor particulars.

Histology of the Membranes.—The pia and arachnoid are composed of delicate bundles of fibrous tissue, upon which lie many small, flattened cells; the outer surface of the arachnoid is covered by a continuous layer of large polygonal, but extremely thin, endothelium. Processes from the pia penetrate the substance of both the brain and cord; these processes carry blood-vessels, and enter into intimate relation

[1] For method of examination see pp. 21 to 25.

with the peculiar supporting structure of the central nervous system, known as the *neuroglia.* From the surface of the arachnoid, especially on each side of the superior longitudinal fissure, bulbous projections occur; these penetrate the dura, and are called the *Pacchionian bodies.* Both the pia and arachnoid are extremely vascular; the blood-vessels are particularly numerous in those prolongations of the former that enter the ventricles and are called the velum interpositum and the choroid plexus. The velum interpositum and the choroid plexus are covered by cuboid epithelial cells, which in the new-born are ciliated.

Both the inner and outer layers of the *dura* are composed of compact bundles of fibrous and elastic tissues—those in the outer being placed transversely to those on the inner coat. This coat contains only a few blood-vessels.

The **brain** comprises those parts of the central nervous system within the cranial cavity; they are the *cerebrum*, the *cerebellum*, the *pons varolii*, and the *medulla oblongata*—the last of which passes into the spinal canal, and becomes continuous with the spinal cord. The brain as a whole is oval in form; the upper surface, although very uneven, presents a fairly regular convexity, while the under surface is somewhat flattened and is much more irregular in appearance. The average weight of the adult brain in man is somewhere near 1350 gm. to 1400 gm., and in woman, 1235 gm. to 1275 gm. While it is true that considerable variation from the foregoing in either direction is not inconsistent with perfect health and even with great intellectual activity, the brains of idiots and of the intellectually feeble are, as a rule, considerably below the average weight.[1]

The **spinal cord** extends from the upper border of the atlas to the body of the second lumbar vertebra, where it terminates in a slender, somewhat conic body called the *filum terminale.* The latter is surrounded by a number of nerve bundles known as the cauda equina. The cord is about forty-five centimeters long and weighs about thirty grams. As a whole, it is irregularly cylindric in form, tapering at its lower end, and forming what is called the *conus medullaris.* Anteroposteriorly it is somewhat flattened; in the lower cervical and upper lumbar regions it swells slightly, producing two areas of increased size, known as cervical and lumbar enlargements respectively. It is divided in front by a groove, called the anterior median fissure; and behind by a septum, termed the posterior median septum (posterior median fissure of some authors). Two quite distinct furrows are situated on the posterior aspect of the cord at the points of exit of the posterior nerve-roots, which is a little external to the median septum; these depressions are called the *posterolateral grooves.* Anterior fissures corresponding to the point of origin of the anterior nerve-roots are described by some authors; recent researches into the location of the different functional tracts of the cord go to show that the anterior and motor columns are physiologically identical; and, further, as there is no sufficient anatomic reason for the belief in a distinct fissure along the line of exit of the anterior roots, its description seems unnecessary.

[1] For more specific statements as to brain weight see Marchand, "Abh d, math. phys. Classe d. Konigl. Sachsischen. Ges. d. Wissensch.," Bd. xxvii, 1902, No. iv, pp. 393–482. Spitzka, "Phila. Med. Jour.," May 2, 1903; also "Science," Sept. 18, 1903, p. 371

The **nerves** arising from the brain and spinal cord consist of a number of separate bundles of nerve-fibers, each of which is incased in a sheathing of fibrous tissue, and all the bundles are connected and surrounded by an outer layer of fibrous tissue which becomes continuous with the neighboring structures.

Histology of the Nervous System.[1]—The entire nervous system, in both man and lower animals, consists of multitudes of extremely delicate fibrils which unite to form a single element (the **neuron**), made up of a cell—the *nerve cell* or *ganglion cell*—and numerous *processes*, one of which, in certain varieties of the cell, becomes the *axis-cylinder* of a nerve, and in this form extends to the point of peripheral distribution; notwithstanding that these cells are all fundamentally identical, certain later differentiations occur, giving rise to morphologic and tinctorial differences, justifying their division into a number of varieties. The nerve elements proper are united by a tissue called the **neuroglia.**[2] The neuroglia consists of numerous small cells between which are multitudes of fibrils that in the adult probably have no connection with the cells; the relation between the fibrils and cells is, however, so intimate that the former have been generally described as processes of the latter, and together they are spoken of as *moss* or *spider cells*, depending upon their individual peculiarities.

The structures composing the neurons and also the neuroglia fibers and cells are believed to be derived from the epiblastic tissues of the body, and should be looked upon as but modified epithelial cells. Although not of connective-tissue origin, the neuroglia in pathologic processes affecting the central nervous system comports itself in a manner resembling the changes occurring in fibrous tissue which constitutes the interstitial structure of other organs; when inflammation or degeneration destroys the functionally higher tissue—ganglion cells and fibers—the neuroglia increases in a way corresponding to the increased connective tissue, for example, in the heart after destructive metamorphoses of the cardiac muscle. The processes affecting the central nervous system, and included under the general term **sclerosis,** are constantly associated with the disappearance of the elements that enter into the formation of neurons and more or less hyperplasia of the sustentacular tissue—the neuroglia.

Ganglion cells are found principally in the gray matter of the central nervous system, but are also present in the sympathetic ganglia, in the ganglia occurring in the course of cerebrospinal nerves, and in the organs of special sense. The cells vary in size from 4 μ to 135 μ. There are a few oval or spindle-shaped ganglion cells, but the vast majority possess irregular forms due to the abundant processes that emanate from them. Cells possessing a single process are called *unipolar* (occur in man in the olfactory mucous membrane); if two processes are present, they are termed *bipolar*; and if more than two, *multipolar*. The processes projecting from one end of a ganglion cell, after proceeding a short distance,

[1] For recent studies dealing with the finer histology of the central nervous system, consult, Dejerine, "Revue Neurolog.," March 15, 1904, p. 205. Bethe, "Deut. med. Woch.," Aug. 11, 1904 Azoulay, "La Presse Méd.," July 23, 1904, and Aug. 24, 1904.

[2] For recent views as to the origin and nature of neuroglia see Hardesty, "Amer. Jour. of Anatomy," July 1, 1904, vol. 3, No. 3

break up into numerous smaller branches, known as *dendrites*, which again subdivide, and their smallest extensions exhibit multitudes of minute projections termed *gemmulæ;* the former have not inaptly been compared to the limbs of a tree, and the latter to the leaves. From some other part, usually the other end of the nerve-cell, another process passes out, which may continue as an *axis-cylinder* of a nerve-fiber, or, after going a short distance, may turn on itself and divide into a number of processes resembling the dendrites arising from other parts of the cell. Cells the processes of which become axis-cylinders are called *cells of the first type*, and those whose processes fail to form axis-cylinders are termed *cells of the second type*. All the peculiarities of the ganglion cells so far mentioned can be brought out with distinctness only by the method of preparation devised by Golgi. This method, as slightly modified by Berkley, is as follows:

To get good results the tissue must be perfectly fresh. It should be hardened in Müller's solution (see p. 31) until it becomes sufficiently hard to admit of fairly thin sections being cut; this requires, at ordinary temperatures, about three weeks. The fluid should be abundant and should be changed daily for the first few days. The tissue is then cut into pieces not exceeding three millimeters in thickness, and placed in the following solution, which should be freshly prepared:

Bichromate of potassium, 3 per cent. solution in water,	100 parts.
Osmic acid (OsO_4), 1 per cent. solution in water, ...	30 "

After three days remove the specimens and imbibe the excess of the foregoing solution with filter-paper; wash for a few minutes in a weak solution of silver nitrate in water. The tissue is now placed in the following solution:

Phosphomolybdic acid, 10 per cent. solution in water,	2 drops.
Silver nitrate, 1 per cent. solution in water, ...	60 c.c.

This mixture should be prepared just before being used. In the mixture the tissue should remain undisturbed for two or three days, or, if desirable, it may be kept indefinitely by adding a few drops of the silver nitrate solution at the expiration of the time mentioned. During the process of preparation it is perhaps better to keep the jars containing the mixture in the dark. Impregnation goes on best at about 25° C. After the foregoing the tissues are placed in absolute alcohol for an hour and are then quickly embedded in celloidin. (See p. 42.) Sections are examined without staining. By this method the nerve-cell and its processes are impregnated with the silver salt and, though unstained, are rendered a uniform brownish-black color. The impregnation is at best very capricious—some of the cells darkening intensely and others in the immediate vicinity, not at all. The neuroglia cells and the fibrils around them are also tinged. Golgi's method is useful only as a stain for the outlines of the cells and their processes, and it therefore becomes necessary to employ other means if it is desired to study the internal structure of these bodies.

The ganglion cells have no distinct cell-membrane. They possess a reticular protoplasm that stains with acid dyes; the greater number of the ganglion cells contain, within the reticulum, a substance that takes

basic dyes intensely. These basophilic masses are called the **tigroid substance** or **bodies of Nissl.** In the great majority of nerve-cells the nuclei do not take basic stains, although they contain a delicate reticulum and a nuclear wall, both of which are acidophilic. As a result of this peculiarity, when the tissues are stained in the usual way, the nucleus appears as an almost unstained or but lightly tinged, round space. Within the nucleus is a nucleolus that stains intensely with basic dyes.

Nissl classifies nerve-cells into (*a*) **karyochromes,** or cells the nuclei of which take basic stains; and (*b*) **somatochromes,** or cells only the protoplasm of which takes the basic dye. The former are comparatively rare, but are found in the olfactory lobe, the cerebellum, and the retina. The latter have been subdivided into several different varieties, depending upon the arrangement of Nissl's basophilic or, as they are also called, chromophilic or tigroid bodies: (1) *Arkyochromes*, or cells in which the chromophilic substance is arranged in rows; (2) *stichochromes*, or cells in which the chromophilic substance is arranged more or less regularly throughout the cell; (3) *gryochromes*, or cells in which the chromophilic substance occurs in fine granules; (4) *arkystichochromes*, or cells in which some combination of the preceding is present. The chromophilic substance is, as a rule, tolerably uniformly distributed throughout the cell; it is, however, worthy of note that just beneath the point where the axis-cylinder process emerges from the cell this substance is largely absent. In conclusion, it should be noted that in many ganglion cells there are small collections of yellowish-brown pigment, situated in the protoplasm just outside of the nuclear wall; the quantity of this pigment increases with age and under pathologic conditions.

Method of Demonstration.—The method first employed for the purpose of demonstrating the previously mentioned peculiarities of ganglion cells was that of Nissl. Blocks of tissue not over one centimeter in thickness are hardened in ninety-six per cent. alcohol. The hardened tissue is removed from the alcohol and gently blotted with bibulous paper; dip the piece of tissue in thick celloidin (p. 42) and attach it to a block prepared as directed (p. 42). Do not embed. Harden the celloidin in ninety per cent. alcohol and section with knife wet in alcohol of the same strength. (Directions for cutting celloidin sections see p. 43.) Preserve sections in ninety per cent. alcohol. The stain used is a soapy solution of methylene-blue (methylene-blue, B.patent), and had best be purchased as prepared by Grübler, who has placed it on the market under the name "Soapy Solution of Methylene-blue" (Nissl). The sections are placed in this solution and heated until bubbles form; they are then washed in a mixture composed of anilin oil (10 parts) and ninety-six per cent. alcohol (90 parts) until differentiation is completed. The sections are now placed on the slide, blotted with filter-paper, and cleared in oil of cajuput. Wash off the oil with benzin and mount in a solution of colophony in benzin; the cement is applied and is gently warmed in order to vaporize the benzin; if the benzin inflames, blow out the flame and continue the warming; finally, when the benzin has been expelled, apply a cover-glass.

In the hands of the author the following method has given better and more uniform results: Fix the tissues, which should be as fresh as possible, in mercury bichlorid solution (p. 34), embed in paraffin (p. 35),

section, and cement to the slide in the usual way; remove the paraffin, wash in alcohol followed by water, and stain sections for from five to thirty minutes—twelve to twenty-four hours will do no harm—in the following solution:

Toluidin-blue, ...	1.5 gm.
Carbolic acid, 5 per cent. solution in water, ...	100.0 c.c.

This solution keeps indefinitely. After staining, thoroughly wash the section in water and differentiate in styrone (p. 49), Unna's glycerin-ether mixture (p. 49), water containing one per cent. acetic acid, or alcohol; again wash with water, quickly dehydrate in ordinary alcohol, and clear in cedar oil. The chromophilic substance is stained a dark blue, the intensity of which depends on the extent to which the differentiation has been carried. (See Remarks on Staining, pp. 48 to 50.)

Thionin is chemically closely related to toluidin blue and may be used in the same manner; the following, however, is recommended: Fix blocks of tissue, not over 1 cm. in thickness, in ten per cent. aqueous solution of formalin for twenty-four hours, dehydrate as directed on page 35, infiltrate in celloidin (p. 42), and section as usual. The sections are transferred to water, from which they are placed in a one per cent. aqueous solution of thionin for from one to five minutes; wash in water until the excess of dye is removed and differentiate in a mixture composed of anilin oil 10 c.c. and absolute alcohol 90 c.c. As soon as the section becomes a pale blue, wash rapidly in ninety-five per cent. alcohol, clear in xylol, and mount in balsam. The color reactions in the stainable substances are practically the same as those given above for toluidin blue.

Neurofibrils.[1]—The studies of Bethe, Apathy, Simarro, Cajal, and others have shown that important components of the neurone are extremely delicate fibrils, some of which are within the ganglion cells and are projected into the axis-cylinders; other fibrils are pericellular. Of a number of methods that have been recommended for the demonstration of these bodies, the following (Cajal) has been found acceptable: Harden specimens about 3 mm. in thickness in 100 c.c. of alcohol containing 1 c.c. of ammonia for from twenty-four hours to three days; wash in distilled water, transfer to 1.5 per cent. aqueous solution of nitrate of silver for from three to five days at 30° C. to 35° C. Complete the reduction of the silver by allowing the specimens to remain for twenty-four hours in a mixture composed of formalin 5 c.c., pyrogallic acid 2 gm., distilled water 100 c c. Infiltrate in paraffin or celloidin and section; dehydrate the sections, clear with xylol, and mount in balsam. The impregnated fibrils are black or brownish-black.

Myelin stains: In the great majority of instances the processes of the nerve-cells that become axis-cylinders of nerves, in a short distance after passing from the cells, are enveloped by a stratum of a peculiar

[1] Cajal, "C. R. Soc. de Biol.," 1903, tome v, p. 1565; and Feb. 27, 1904, p. 368; "Centralbl. f. allg. Path. u. path. Anat.," 1904, No. 3, p. 122; also "Trabajos del laboratorio de investigaciones de la Universidad de Madrid," Dec. 28, 1903, pp. 129–221. Chilesotti, "Zeit. f. Wissensch. Mikros. u. f. Mikroscopische Technik," Dec. 2, 1902, p. 161. Marinesco, "Revue Neurolog.," May 15, 1904, p. 405. Biart, "Med. Record," August 6, 1904, p 217. Bielchowsky, "Jour. f. Psychol. u. Neurol.," 1904, Bd. 3, fasc. 4, p. 30.

substance, nearly related to fat, and known as *myelin* or the *white substance of Schwann.* After this substance surrounds the axis-cylinder it is difficult so to stain the latter that it can be differentiated from the tissues with which it happens to be in contact. As the myelin sheath accompanies it almost to its termination, attention has been directed to staining this covering rather than the axis-cylinder itself; coloration of the myelin sheath is accomplished in a most beautiful manner by the methods of Weigert or some modification of his processes.

Blocks of tissue 1 cm. to 2 cm. in maximum diameter are hardened in Müller's fluid until they acquire a dark brown color; this generally takes from six to eight weeks, and may be slightly hastened by keeping the tissues warm (30° C. to 35° C.) and frequently changing the solution. Rinse off the excess of Müller's fluid, dehydrate (p. 35), and infiltrate with celloidin (p. 44). The sections should be relatively thick, 20 μ to 30 μ; they are rinsed in water and transferred to stain possessing the following composition: Dissolve 10 gm. of hematoxylin (crystals or powder) in 90 c.c. of absolute alcohol; prepare the stain to be used by adding 10 c.c. of the alcoholic solution of hematoxylin to 90 c.c. of water containing 1 c.c. of a saturated aqueous solution of carbonate of lithium. The alcoholic solution of hematoxylin should have been ripened by exposure to the light for at least two weeks; the saturated aqueous solution of carbonate of lithium may also be kept on hand, but the final stain must be freshly prepared from the stock solutions. Sections are left in the stain for twenty-four hours, after which they are removed and thoroughly washed in water. The differentiation is accomplished in a solution composed of borax 2 gm., ferricyanid of potassium 2.5 gm., water 100 c.c., which, for the beginner, had best be diluted with an equal volume of water. The sections are lightly agitated in the differentiating solution until the white and gray substances are clearly differentiated, the length of time necessary varying according to the strength of the differentiating solution used. The sections are then washed through several changes of water, dehydrated in ninety-five per cent. alcohol, cleared in a mixture called carbolxylol,—which consists of carbolic acid crystals 1 part, xylol 3 parts,—and, finally, they are mounted in balsam. When stained by the method just given, all parts of the section not colored by the hematoxylin are yellowish, and if it is especially desired to photograph the specimen, Pal's method of decolorization may be used. The tissue is prepared by the method given above, and the sections cut and stained with the hematoxylin-carbonate of lithium-water mixture as already directed. They are then washed in water and transferred to a solution composed of potassium permanganate 0.25 gm. and water 100 c.c., in which the gray substance turns a brownish-yellow. The time required for this stage is usually brief, varying between thirty seconds and five minutes. The sections are at once transferred to a solution consisting of oxalic acid 1 gm., sulphite of potassium 1 gm., water 200 c.c. In a few seconds the gray matter becomes colorless and the specimen should be quickly placed in water, several changes of which are necessary to remove the last traces of the differentiating solution. Finally each section is dehydrated in ninety-five per cent. alcohol, cleared in carbolxylol and mounted in balsam. By the foregoing myelin sheath stains this substance, when normal, is tinged a deep purple or almost black, and the presence

of degenerative or necrotic processes is indicated by the absence of, or abnormality in the myelin reaction.

In addition to the purely nervous elements of the central nervous system, there is a supporting structure, as has been before remarked, known as the **neuroglia.** This consists of numerous small cells, termed glia cells, and a tangled mass of fibrils that closely surround the cells and the various nerve elements; it is not probable that these fibrils are really connected with the glia cells. The latter are seen after preparing tissues in the ordinary way, but the fibrils are brought out only by special methods,[1] of which that devised by Mallory is recommended. The first step in this process is the preparation of phosphotungstic hematoxylin, which is made by dissolving 0.1 gm. of hematoxylin in 80 c.c. of water, using heat if necessary, and, when cool, adding 20 c.c. of a 10 per cent. aqueous solution of phosphotungstic acid (Merck). It is usually necessary to ripen this mixture artificially by the addition of 0.2 c.c. of hydrogen peroxid. The tissues are fixed in 10 per cent. aqueous solution of formalin for four days and are then placed, for an equal length of time, in a saturated aqueous solution of picric acid. From the latter mixture they are transferred to a five per cent. aqueous solution of bichromate of ammonium, in which they should remain from three to four weeks at room-temperature or four to six days at 37° C.; dehydrate as directed on page 35 and imbed in celloidin (p. 42). The sections are transferred to a solution consisting of potassium permanganate 0.5 gm., water 100 c.c., for twenty to thirty minutes; they are then washed in water and placed in a five per cent. aqueous solution of oxalic acid for from one to two hours. Wash thoroughly in water and stain in the phosphotungstic acid hematoxylin for from one to two days, wash lightly in water and transfer to a freshly prepared twenty per cent. alcoholic solution of ferric chlorid for from ten to twenty minutes. The latter solution must be removed by thorough washing in several changes of water, dehydrate in ninety-five per cent. alcohol, clear in oleum origani cretici and mount in xylol balsam. The neuroglia fibers are stained a transparent blue and the nuclei and any fibrin present are similarly tinged.

The *white substance* of the central nervous system consists of axis-cylinders surrounded by myelin, and imbedded in neuroglia. The *gray matter* is composed of ganglion cells and their processes, bound together by neuroglia. The ganglion cells of the gray substance show certain peculiarities in different situations; as examples of this may be cited the arrangements and especial characteristics of the cells of the gray matter of the cerebrum, of the cerebellum, and of the spinal cord. In the cerebral cortex the gray matter begins just beneath the pia. The outer layer of this structure contains only protoplasmic processes, derived from the underlying pyramidal cells, and neuroglia, and is called the *molecular layer;* immediately beneath this is the layer of *small pyramidal ganglion cells.* Underlying and adjacent to the last-named stratum is another layer, also resembling the first, but the ganglion cells are longer than in the layer last referred to, and are called the *large pyramidal cells.* Still deeper, and forming the deepest stratum of gray matter, is a fourth layer, in which the nerve cells are irregular in form,

[1] Mallory and Wright, "Pathological Technic," 1904, pp. 348 to 353. See also Bartel, "Zeit. f. Wissen. Mikro.," Aug. 1, 1904, p. 18.

and are hence termed *polymorphous.* From most of these cells axis-cylinders of nerves arise.

The outer part of the gray matter of the cerebellar cortex is also termed the *molecular layer.* In it are two kinds of nerve-cells—the small, occupying the outer part of the layer, and the *large* or *basket cells*, lying more deeply. Beneath the molecular layer is a very thin stratum containing the *cells of Purkinje.* These cells are very large, and send off abundant protoplasmic processes; they are unique in that they are the only ganglion cells in the cerebellum from which arise axis-cylinders that become nerves. Beneath the molecular layer is a *granule layer* containing numerous cells, some of which are slightly larger than others. The nuclei of these cells stain intensely, and hence belong to the group of cells called karyochromes.

The anterior cornua in the spinal cord also contain numerous large multipolar ganglion cells. From the seventh cervical to the third lumbar segments a group of nerve-cells lies in the inner part of the neck of the posterior horn and constitutes the *column of Clarke.* The neuroglia cells are very numerous immediately around the central canal of the cord, which area is often called the *substantia gelatinosa centralis.*

The arteries of the central nervous system are abundantly supplied with elastic tissue, the contractility of which, under normal conditions, is not lost with age; for this reason it is thought that ordinarily the mind does not correspondingly fail along with the strength and other bodily functions in old age.

The **nerves** passing from the brain and cord consist of numerous bundles of nerve-fibers inclosed in a common sheath of fibrous tissue, called the *epineurium.* The individual bundles are surrounded by a sheath, continuous with the foregoing, termed the *perineurium;* the last-named structure sends processes between the nerve-fibers, which support the blood-vessels, and constitute the *endoneurium.* Around each individual nerve-fiber there is a delicate connective-tissue membrane, known as the *primitive sheath*, within which is the myelin covering that surrounds the axis-cylinder. It should be remembered, however, that the myelin sheath is not present in the nerves of the sympathetic system, and is occasionally absent in the cerebrospinal nerves. When the myelin sheath occurs, it is interrupted at regular intervals; such interruptions are known as the *constrictions* or *nodes of Ranvier;* at these points the axis-cylinder and the primitive sheath come directly in contact. When nerves branch, they always do so at these constrictions. Just before the nerve ends the myelin sheath terminates, and the axis-cylinder is continued onward inclosed only in its primitive sheath.

MALFORMATIONS OF THE BRAIN AND SPINAL CORD.

The brain and spinal cord take their origin from the formation and subsequent invagination and closing-over of a depression in the *superior germinal layer*, known as the *medullary groove.* After closing, this groove forms a cylindric canal, known as the *medullary tube* (*neural tube*), the walls of which are formed by the invaginated *epiblastic* tissues from the superior germinal layer just mentioned. This tube occupies the position in the embryo corresponding to that of the future spinal

cord and brain. The cord is formed from the posterior part of the tube, while the brain is developed from three saccular dilatations, known as *vesicles*, which form toward its anterior end; the first and third of these vesicles are each later subdivided into two, making, in all, five vesicles, from which the different parts of the brain take their origin. The epiblastic tissues constituting the covering of the medullary tube especially multiply, so that the walls of the tube are greatly thickened and the developing cells become specialized into the peculiar component elements that go to make up the central nervous system. This thickening encroaches on the lumen of the tube, but a small canal in the center, and much larger cavities in the brain, persist throughout life; the former is called the *central canal of the cord*, and the latter are known as *ventricles*. These cavities are all lined by epithelial cells, which in early life are ciliated.

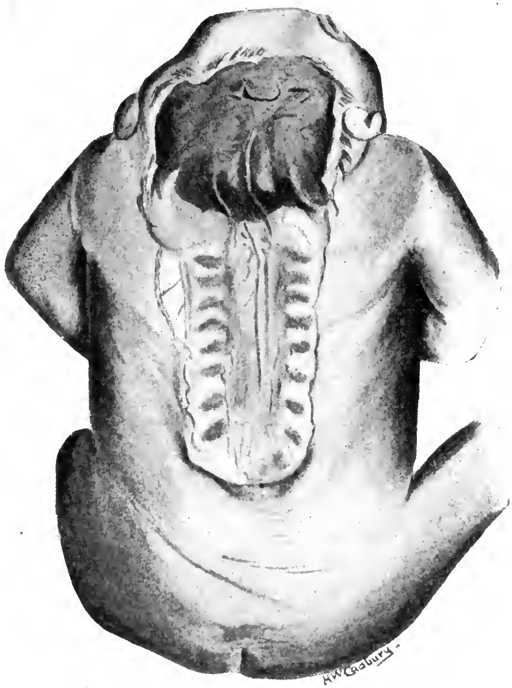


FIG. 405.—CRANIORRHACHISCHISIS TOTALIS. There is a small amount of brain substance present and a few shreds of nervous tissue in the spinal grove.

In normal development the medullary groove is entirely cut off from the superior germinal layer, from which it springs. It occasionally occurs that the groove is not closed, and a part or even all of it remains patent; under these circumstances neither the bony arches of the vertebræ nor the posterior and upper cranial bones develop in the situation where the groove fails to close. In these cases malformations of the brain or cord result, the character of which depends on the situation, kind, and extent of the areas of the groove not closed over. We possess no accurate information as to the cause of these conditions; the general aspects of teratogenesis are discussed on page 60.

Craniorrhachischisis Totalis.[1]—When the entire medullary groove remains patent, neither the skull nor the vertebræ close posteriorly; the resulting condition is called craniorrhachischisis totalis. A fetus that at birth presents this malformation is found to possess, on the dorsal surface of its trunk, a wide, shallow depression, uncovered by skin, occupying the median line, which, passing upward, becomes expanded over the posterior part of the head. In the median line of this fissure, flattened

[1] Given, "Proceed. Path. Soc. of Phila.," June, 1902, n. s., vol. v, p. 266. Vurpas and Leri, "C. R. Acad. des Sci.," July 20, 1903.

out over the bodies of the vertebræ, are found varying amounts of a delicate, soft, and very vascular tissue, consisting of the rudiments of the brain and cord; in rare instances no nervous tissue can be demonstrated. In many cases, however, the anterior part of the brain is fairly well developed. The external surface of the fissure is covered by columnar epithelium, which is continuous on each side with the squamous epithelium of the skin, and corresponds to the epithelial lining of the central canal of the cord and the ventricles of the brain. Between the rudimentary nerve substance and the bodies of the vertebræ are the highly vascular tissues of the pia and arachnoid, and, still more deeply, a fibrous membrane—the dura; between the arachnoid and dura there is often a flattened cavity, containing fluid, and corresponding to the subdural space. In total craniorrhachischisis the eyes project prominently from the flattened skull, but generally neither they nor the nose are greatly displaced. The spinal column is always abnormally curved forward.

Much commoner than failure of the entire medullary tube to develop are limited defects restricted to small areas of either the cranial or spinal portions. These local anomalies can be more easily understood from an examination of the spinal malformations; and as they, in a way, lead up to the more complex but analogous condition occurring in the brain, they will be first considered.

Rhachischisis Totalis (Holorrhachischisis).—In case the entire spinal portion of the groove remains patent the condition that results is known as rhachischisis totalis. With the exception of the fact that the brain is not involved, this condition differs in no way from craniorrhachischisis totalis, and a separate description is therefore unnecessary.

Rhachischisis Partialis (Merorhachischisis).—When only a part of the spinal portion of the medullary tube fails to close, the resulting condition is called rhachischisis partialis; this is most frequent in the sacrolumbar and cervical regions, but the intermediate parts are also occasionally affected. As in total rhachischisis, the rudimentary spinal cord is exposed—owing to a failure of development on the part of the vertebral arches—in the situations where the groove remains patent, and the anatomy of the condition is essentially that of the more pronounced malformations. The spinal cord in the affected area is spread out on the vertebral bodies, forming an irregular layer of soft, red, and very vascular tissue, which connects the two ends of the normal cord, or, in some instances, forms the termination of the cord below; in many cases, however, this intervening rudimentary substance is present to a very limited degree, or may be entirely absent. When nervous structures are present, they are covered by columnar epithelial cells, and lie upon a membrane that corresponds to the pia of the normal cord. The edges of this pial membrane are usually exposed at the lateral margins of the spinal substance, and, therefore, intervene between the latter and the skin of the back. Near the upper or lower margin of the defective cord, or at both points, there is a small depression, which corresponds to the closed end of the central canal of the normal cord beyond. Between the pia, on which the undeveloped cord lies, and the bodies of the vertebræ are the arachnoid and dural membranes, with the intervening spaces filled with liquid, as in the normal vertebral canal.

Myelomeningocele.—When the condition just described exists in

infants or children, especially if it be, as is generally the case, toward the lower end of the spinal column, the subarachnoid space frequently dilates as a result of the long-continued pressure of the contained fluid on the delicate pia, which, with the rudimentary cord, forms the external wall of the cavity. In the beginning the structures just mentioned, with a few delicate strands of tissue from the arachnoid, form the entire outer wall of the tumor, but as the swelling increases the neighboring skin becomes a part of its external support. This condition is technically known as **myelomeningocele.** When the myelomeningocele is situated at the end of the cord, the tumor shows on its convex surface a slight depression, which corresponds to the closed end of the central canal of the cord previously referred to.

Meningocele.—This is another variety of malformation closely resembling in appearance the one just considered; it, however, differs from myelomeningocele, in that it appears not to depend on an abnormal development of the medullary part of the tube, but is due to a deficiency of the bony wall of the vertebral column. Under these circumstances there is sometimes formed a saccular tumor, the walls of which are composed of the external layer of the arachnoid and the dura, external to which are the soft parts covering the particular area involved. Meningocele is most frequent in the sacral region, where defects in the vertebræ are most common. In rare instances the defect is in the body of the vertebræ, in which case the sac projects forward; it is thus possible for the tumor to protrude into the abdominal cavity.

Myelocystocele (Hydromyelocele).—When there are deficiencies in the vertebræ, saccular tumors are in rare instances developed having their origin in accumulations of fluid in the central canal of the cord. In their outward appearance they closely resemble meningocele, but, of course, differ in that the inner wall of the tumor is composed of the compressed substance of the cord. Myelocystocele in most instances occurs in connection with lateral clefts in the vertebræ, and defects in their bodies are also often present. Shortening of the trunk is a frequent consequence. When there is no defect in the vertebral column, the central canal is sometimes dilated as a result of increased amounts of fluid within (**salpingomyelus; hydromyelia**); the dilatation may be diffuse. Meningocele and myelocystocele sometimes occur together; the condition is known as **myelocystomeningocele.**

Spina bifida is the common clinical term for designating any of the foregoing conditions associated with the formation of tumor-like masses. In the condition called **spina bifida occulta**[1] there is no external evidence of the partial absence of the bony wall nor any protrusion. The condition is sometimes associated with an abundant growth of hair (hypertrichosis sacralis), usually situated in the sacral area.

Malformations of the spinal cord without accompanying defects in the vertebræ are quite unusual, and are rarely of a pronounced character. However, the cord is sometimes abnormally short and slender (**micromyelia**), and occasionally exhibits partial duplications (**diastematomyelia**). Asymmetries also occur.

Defects in the nerve-roots are comparatively infrequent.

Primary defective development of the nerve-tracts has also been

[1] Schein, "Budapesti Orv. Ujsag," 1904, No. 7; also "Gyogyaszat," 1904, No. 29. Voelcker, "Münch. med. Woch.," Oct. 13, 1903, p. 1802.

observed; this is of interest, in that it may become the starting-point of disease in later life.

An anomalous condition of the spinal cord, known as **heterotopia,** is occasionally observed; in this abnormality the gray substance does not bear its normal relation to the white matter, but is more or less scattered through it.

The **malformations of the brain** in general correspond to those occurring in the cord; the causes, however, of the various defects are not so well understood. In addition to craniorrhachischisis, which has been described, there is no doubt that many of the other cerebral malformations owe their origin to permanent patency of the medullary groove; it is equally clear that others result from fluids accumulating in the cranial

FIG. 406.—SPINA BIFIDA.

cavity of the embryo, and causing rupture of the bony walls. There are doubtless also other causes that occasionally produce these conditions, the real nature of which, however, is largely a matter of conjecture.

Cranioschisis is a condition produced by the same cause as, and closely related to, craniorrhachischisis, and corresponds in the brain to rhachischisis of the cord. Here, also, the cranial vault is to a greater or less extent absent, and on the basal bones lies a reddish mass of tissue, which may contain rudimentary brain substance, or, more rarely, none at all (**anencephalia**). This reddish mass is covered by columnar epithelium, which, as in rhachischisis, becomes continuous with the surrounding skin. The base of the skull is very small, while the jaw and eyes project prominently, giving to the head a very characteristic appearance; for this reason it is sometimes spoken of as *cat-head* or *toad-head*.

It occasionally happens that one or more of the gyri fail in a greater or less degree to develop, leaving, at the point, a depression that may extend to the ventricle. These cavities of the cerebral cortex are most common in the central and parietal lobes. They have received the name of **porencephalia.**[1] Cavities very similar to these may occur in the cerebral cortex as the result of disease; such condition is termed **pseudoporencephalia.**

Circumscribed errors in development occur in the skull analogous to those that are seen in the spinal column, but differing from them in some minor details. They are most frequent in the median line, and in the majority of instances are situated in the posterior portion of the skull.

Encephalomeningocele corresponds to myelomeningocele; it consists of a saccular tumor of varying size projecting from the skull at some point—usually the occipital region. On section its walls are found to consist of the outer layer of the arachnoid, the dura, and the skin and a hernial projection of brain-substance, which at the apex of the tumor is closely adherent to the meningeal coverings, these being, in turn, firmly united to the skin; a small scar, or, sometimes, a minute mass of reddish tissue, representing the point where the medullary groove failed to close, or was last obliterated, will usually be found on the external surface of the skin, corresponding to the point of adhesion of the membranes below. More or less fluid is present in the sac, usually between the brain and the adjacent wall.

Meningocele.—Should brain-substance be entirely absent from such a saccular tumor as has just been described, the condition is called meningocele.

Encephalocele.—The term encephalocele is used to designate those saccular tumors springing from the skull that contain brain substance as well as the meninges, but no fluid. They are closely allied to the conditions previously referred to.

Accumulations of fluids not infrequently occur in the ventricles of the brain corresponding to myelocystocele, salpingocele, and hydromyelia; the condition is known as **congenital internal hydrocephalus.**[2] This abnormality is, as a rule, not compatible with health or long life, but infants so afflicted not infrequently live for a number of years, and complete recovery sometimes occurs. When an infant, Thackeray is said to have been hydrocephalic, and the recent[3] examination of the brain of Menzel, the great German painter, has shown that he, like Helmholtz, had hydrocephalus. This condition is associated, when at all extreme, with enlargement of the skull, greatly interfering with the normal ossification of the bones composing it; in some instances the intracranial pressure becomes so great that rupture occurs, though immediate death does not necessarily result. It has been mentioned that some of the malformations of the brain are brought about by such a rupture occurring *in utero.*

Small portions of the ventricles of the brain are sometimes separated from the main cavities by adhesions. When this happens, the isolated cavity becomes greatly distended, as a result of accumulations of fluids

[1] See Shirres, "Studies from the Royal Victoria Hospital, Montreal," vol. i, No. 2, Jan., 1902.
[2] See Spiller, "Amer. Jour. of Med. Sci.," July, 1902.
[3] Berlin Correspondent of "Brit. Med. Jour.," Feb. 18, 1905, p. 384.

within; portions of the fourth ventricle and the posterior horns of the lateral ventricles most frequently exhibit this abnormality. A like process sometimes occurs in the fifth ventricle.

Cyclopia (Synophthalmia).—When arrest of development involves the anterior part of the brain and frontal area of the skull, a malformation known as cyclopia sometimes occurs, mainly characterized by the fact that there is only one optic nerve, both eyes being fused into one organ that usually occupies a cavity in the center of the forehead; all the face-bones except the upper jaw may be absent. (See p. 564.) The nose often fails to develop; when present it is malformed, and occupies a position above the eye. Sometimes the anterior portion of the brain fails to divide into two normal hemispheres, and the ventricle is occasionally so dilated that the brain appears as a large cyst (**cyclocephalia**). In less severe forms of this condition the two eyes may be fused in part only, or may, without union of any kind, occupy the same cavity.

Arhinencephalia.—This condition, with the exception that the nose is always absent, and also the olfactory bulbs, is practically identical with cyclopia; it has been shown, however, that arhinencephalia may exist without very marked malformation of the eyes. This abnormality is often accompanied by cyclocephalia; absence of olfactory nerves; fissure of the upper lip and palate; defective development of the intermaxillary bone and nasal septum; malformations of the heart, great vessels, and auricular appendages; umbilical hernia; supernumerary fingers and toes; and defects of the diaphragm.

Microcephaly may be associated with arhinencephalia. It is characterized by the following peculiarities: the brain is very small; its convolutions are poorly outlined and much less numerous than usual; everything about the brain attests the fact that it is undeveloped; the skull is small and its bones exhibit many abnormalities of ossification, or numerous Wormian bones may be present. If any or all of the ventricles are dilated, the condition is known as **hydromicrocephaly.**

Partial hypoplasia of the brain may also occur. It is most common in the cerebrum and cerebellum, though it may involve other parts of the central nervous system. If the gyri are abnormally small and numerous, the condition is called **microgyria.**

Hypertrophy of the brain may occur, but the condition is rare. Under these circumstances the normal elements present in the brain are to a greater or less extent increased in number.

Heterotopia[1] of the gray matter is a condition analogous to that observed in the cord: the gray matter is present here and there in the white substance, giving it a mottled appearance.

DISEASES OF THE MEMBRANES OF THE BRAIN AND SPINAL CORD.

Diseases of the membranes of both the brain and cord will be considered together, for not only are they practically identical in their anatomy, and very closely related by continuity of surface, but they are affected alike in disease, and oftentimes simultaneously. As the dura may be diseased and the membrane that lies internal to it may be to all intents and purposes normal, and vice versa, it becomes necessary to consider their pathologic conditions separately.

[1] Alice Hamilton, "Amer. Jour. of Anat.," Sept. 15, 1902, vol. i.

The **cerebrospinal fluid** surrounds the brain and cord and occupies the normal cavities of these organs; normally it is clear, alkaline in reaction, possesses a specific gravity of 1.005 to 1.010, and contains traces of proteids and hydrocarbons. Recent studies in cytodiagnosis[1] have shown that a microscopic examination of this liquid may be of great aid in diagnosis, and that under a number of conditions the pressure is raised. When hemorrhage, either traumatic or pathologic in origin, involves the brain or meninges, erythrocytes can usually be demonstrated in the cerebrospinal fluid. The lymphocytes are increased in chronic inflammations and tumors, and polymorphonuclear leukocytes are particularly abundant in cerebrospinal meningitis and other infections of the meninges in which pyogenic bacteria are present. It may be possible to demonstrate specific organisms in the cerebrospinal fluid; the effort is always worthy of trial in suspected epidemic meningitis, tuberculous meningitis, and other inflammations affecting the meninges. The parasite believed to be the cause of syphilis (p. 174) and the trypanosoma of sleeping sickness (p. 183) have been found. The pressure under which the fluid exists is raised in certain forms of uremia, in eclampsia, and in some, but not all, inflammatory conditions; normally this pressure is between 65 mm. and 100 mm. of water, and under pathologic conditions the tension may rise to 500 mm. or 600 mm., and occasionally higher.

The Dura Mater.

Circulatory Disturbances.—*Active hyperemia* occurs in the dura in the first stages of inflammation. *Passive hyperemia* would be induced by obstruction, from any cause whatsoever, of the larger veins or sinuses. *Hemorrhages* are usually the result of injury, but may occur in scurvy, and, occasionally, in infectious diseases. **Sinus thrombosis**[2] of the cerebral dura is, on the whole, an infrequent condition. It may result from infective, inflammatory, or neoplastic processes involving the sinuses, in which case it is said to be secondary. The most important and probably the most frequent form of the affection is that accompanying suppurative lesions of the middle ear or mastoid and is manifested by a thrombosinusitis which often gives rise to embolic processes (see thrombosis, p. 270). In individuals debilitated by disease, and especially in the young and aged, the formation of thrombi within the sinuses occasionally occurs.

Inflammations of the dura, or **pachymeningitis,** may be acute or chronic, and suppurative, fibrinous, or productive in character.

Suppurative pachymeningitis is the most frequent variety of inflammation of the dura; it may be acute or chronic. It is, in the majority of instances, secondary to suppurative disease of the middle ear, but may occur after injury or disease of the skull or vertebræ. This form of meningitis is sometimes caused by suppuration of thrombi in the various sinuses, and is rarely secondary to inflammations of the pia and arachnoid.

The membrane is swollen, owing to the presence of increased amounts of fluid, and is somewhat reddened. Microscopically, the tissues are

[1] See references on p. 291, where the subject of cytodiagnosis is discussed, also consult Erl, "Dublin Med. Jour.," Dec., 1903. Also Gordon, "Amer. Med.," July 22, 1905.

[2] See Spiller and Camp, "Jour. Amer. Med. Assoc.," Sept. 24, 1904, p. 88.

found to contain many polymorphonuclear leukocytes, swollen connective-tissue cells, and varying numbers of bacteria.

Chronic internal pachymeningitis[1] is a peculiar variety of inflammation affecting the dura of the cranial cavity; its causes are not understood. Of the dura the inner surface alone is involved, and in some instances the inflammation extends to the pia and arachnoid; the contignous bones of the skull are sometimes diseased. Sometimes the entire surface of the cranial dura is affected, and occasionally the condition is restricted to one or more small areas, on one or both sides of the brain. In the beginning stages of the disease there forms, on the internal surface of the dura, a thin false membrane, consisting of fibrin, in which are many connective-tissue cells and a few leukocytes. At a later stage the fibrinous mass is permeated by blood-vessels; these vessels very frequently rupture, giving rise to hemorrhage, and justifying the name **hemorrhagic pachymeningitis,** which is generally employed to designate this condition. The hemorrhages are usually small, but sometimes are sufficiently large to exert considerable pressure on the brain; when profuse, they produce tumor-like masses called hematomata. At a later stage more or less fibrous tissue is formed in the false membrane, and the condition assumes the form of a productive inflammation. Sometimes the false membrane is, in a manner, absorbed, but the fibrous tissue remains as a scar. Discoidal cysts containing blood, or, in old cases, almost clear serum, are occasionally observed. Barratt does not believe that the process is of bacterial origin, but that it depends upon abnormal formation of fibrin within the vessels, the walls of which subsequently weaken and permit hemorrhage. Pressure gives rise to cortical atrophy and sometimes cellular infiltration. The disease is most common among the insane, and occurs in men about twice as often as in women. If the condition be once inaugurated, complete recovery probably never occurs; periods of improvement, followed by exacerbations, commonly occur.

Tuberculosis of the dura is secondary to tuberculosis of the inner membranes, or follows tuberculosis of the bones of the skull or vertebræ. The tubercles present the same nodular characters, with areas of caseation, that are seen in tuberculosis of other parts of the body.

Syphilis of the dura alone is quite rare. It occurs as local thickenings of the membrane, composed of collections of lymphoid and plasma cells, and an increase in the amount of fibrous tissue; at a later stage calcareous deposits sometimes form in these areas. The blood-vessels generally show evidence of endarteritis. Within the affected tissue small masses of caseous material are occasionally observed.

Tumors.—Endothelioma is the most frequent tumor of the dura and occasionally attains considerable size. Spindle-cell sarcoma and other forms of sarcoma are sometimes seen. Psammoma, fibroma, and secondary carcinoma occur; osteomata and enchondromata have been reported.

[1] Barratt, "Brain," 1902, Part II, p. 181. Munro, "Chicago Clin. Recorder," Dec., 1902, p. 381. Courtney, "The Alienist and Neurologist," Feb., 1903 Hertle, "Wien. klin. Woch.," Aug. 6, 1903, p. 919. Fischer, "Zeit. f. Heilk.," 1904, Bd. xxv, H. 10.

The Pia and Arachnoid.

Circulatory Disturbances.—*Active hyperemia* is produced by any irritant acting on the membranes. It is, therefore, of course, always present in the beginning of inflammations.

Passive hyperemia is the result of thrombosis of any of the large intracranial vessels, and is also produced by tumors and exudations pressing upon and obstructing the veins. Under these conditions the hyperemia may be more or less localized. A more general condition of hyperemia of the passive kind is caused by obstructive diseases of the heart or lungs that interfere with the onward flow of the blood.

These abnormal states of the membranes are, of course, identified by the fact that there is more blood present within the meningeal vessels than is normal. The recognition of these conditions, even postmortem, is often difficult, for after death the blood gravitates to the most dependent situations. If, therefore, the head of the subject be placed lower than the body for any length of time, the brain, on section, presents an appearance of extreme congestion. This may also occur to a limited degree if the skull be opened before the other cavities of the body. *Anemia of the meninges* occurs in general anemic conditions and when there is narrowing of the vessels that carry the blood into the parts. In cerebral ischemia from any cause the blood in the meninges is less than in health.

Edema of the brain occurs under those conditions in which the walls of the blood-vessels become so damaged that they permit the fluids of the blood to pass into the surrounding parts more rapidly than the lymphatics can remove them. It is common in inflammations, and as a result of the pressure on the vessels by morbid growths; an excess of fluid is also present in the meninges after death from alcoholism, nephritis, and chronic cardiac disease. The condition is characterized by the presence of swelling, and on section more fluid exudes than is normally the case; the membranes generally possess a translucent, gelatinous appearance. If the ventricular plexuses—which, it will be remembered, are but extensions of the pia—become inflamed or otherwise diseased in such a way as to cause increased permeability of the walls of the blood-vessels within them, it must follow that the quantity of fluids in the ventricles will be increased, causing distention and enlargement of the ventricles; the condition is called **acquired internal hydrocephalus.**[1] Inflammatory thickenings due to tuberculosis, syphilis, or other causes which affect the membranous roof of the fourth ventricle and involve Magendie's foramen or other foramina in such a way as to prevent fluid from escaping from the ventricles, lead to its accumulation in these cavities. Galatts believes that every instance of hydrocephalus not explained by some other condition is due to syphilis. Some cases are traumatic. In this connection it may be remarked that in conditions giving rise to atrophy or necrosis of any part of the brain the space made vacant by the process is filled with fluid. The condition is termed *hydrops ex vacuo.*

Inflammation of the pia and arachnoid is called **leptomeningitis,** or simply **meningitis.** Like inflammations of the dura, it may be *acute* or

[1] Weber, "Brain," Spring, 1902, p. 145. Galatts, "Wien. klin. Woch.," 1904, No. 25. Southard and Roberts, "Jour. of Mental and Nervous Diseases," Feb., 1904, p. 73.

chronic, and *suppurative*, *fibrinous*, or *productive*. Etiologically this form of meningitis may be due to pyogenic cocci, the pneumococcus, anthrax bacillus, typhoid bacillus, colon bacillus, influenza bacillus, bacillus of glanders, pneumobacillus of Friedländer, Bacillus pyocyaneus, the tubercle bacillus, actinomyces, and a number of other organisms; an acute meningitis of this type occasionally accompanies syphilis. Meningeal inflammation due to injury (**traumatic meningitis**) belongs with this group; it is clearly an infection. As in inflammations of other serosæ (p. 456), the acute forms are likely to be suppurative or fibrinous, or a combination of the two, while in the chronic cases fibrous tissue is produced, and the inflammation is consequently spoken of as productive. In a certain proportion of cases the membranes of the brain and cord are affected, but more frequently the inflammation is confined to those of the cranial cavity; rarely, the diseased condition occurs in the membranes of the cord only. There is a form of basic meningitis largely restricted to the posterior fossa and called **posterior basic meningitis.** Still believes that it is specific and due to a special organism which he describes; Koplik[1] has shown that it may occur during epidemic cerebrospinal meningitis and be due to the Diplococcus intracellularis meningitidis. In the great majority of cases meningitis may be looked upon as merely incidental, it being secondary to pathologic conditions in other parts of the body, or due to morbific influences that affect the body as a whole. The exception to this is the epidemic form, which is an entirely separate and distinct disease; this variety will therefore be considered independently. What we may term, for convenience, *incidental meningitis* may be divided into acute and chronic forms.

The acute form is more common in children than in adults. Investigations within recent years have shown that in quite a number of the diseases that predipose to meningitis the same micro-organism is responsible for both conditions. Belonging to this group are the meningeal inflammations occurring in connection with general tuberculosis, typhoid fever, erysipelas, pneumonia, and bubonic plague; it may result from septicemia, whether this comes from septic wounds, septic puerperal processes, the softening of clots, ulcerative endocarditis, malignant pustule, abscesses or other internal suppurations. To this list should be added septic processes in the vicinity of the brain, where there is extension of the inflammation into the meninges from contiguity of tissue, such as wounds of the scalp, erysipelas of the scalp or nasal cavities, glanders, actinomycosis, disease of the internal ear or mastoid, septic inflammations of the eyes, caries of the cranial bones or vertebræ, and abscess of the brain or cord.

Inflammation of the meninges also occurs in connection with such diseases as measles, scarlet fever, smallpox, and sunstroke. Excessive mental work is alleged sometimes to act as an exciting cause, but this is doubtful. Meningitis may also, of course, be the result of injuries to the skull. Lastly, in a certain proportion of cases meningitis occurs without antecedent disease. When it results as a complication of suppurative diseases, the same micro-organisms that gave rise to the primary condition are usually found in the meninges.

Morbid Anatomy.—The inflammation may be limited to some part, as the meninges of the base, or of the convexity of the brain, especially if the

[1] "Amer. Jour. of Med. Sci.," Feb., 1905.

lesion be due to sunstroke or to local adjacent disease, and occasionally these parts are alone involved, even when the process is the result of general conditions. The basal portion, except in tuberculosis, is not commonly the only part affected. More frequently, evidences of the inflammatory process can be seen over the entire meninges. In the cord the inflammation is usually widespread.

The appearance of the membranes differs somewhat, depending upon whether or not the process be of a suppurative kind. In the former class of cases, which usually follow suppurative diseases, the membranes are distinctly reddened, swollen, and opaque; they are

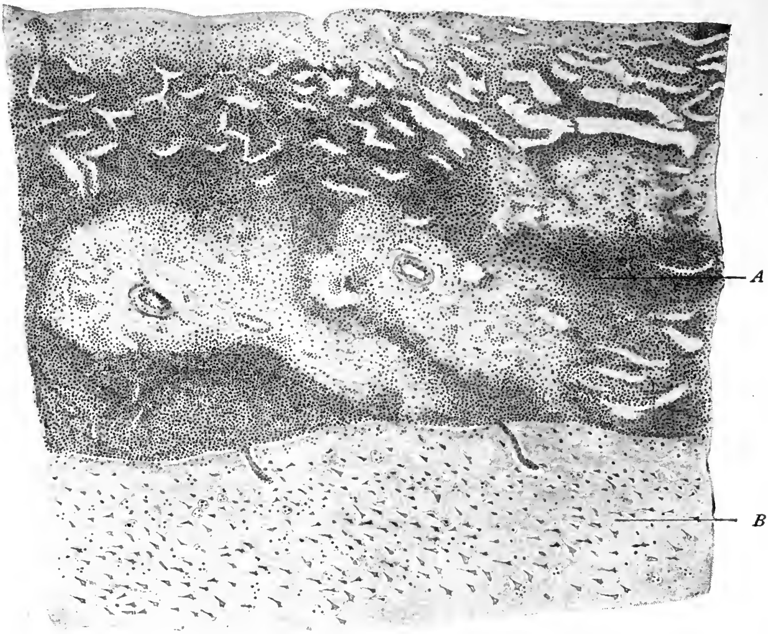


FIG. 407.—SECTION OF CEREBRAL CORTEX AND MENINGES FROM A CASE OF SUPPURATIVE MENINGITIS. *A*. Pia-arachnoid infiltrated with pus-cells. *B*. Normal brain-substance beneath.

bathed in a yellowish-white, yellowish or greenish-yellow, and sometimes fetid pus. The purulent collections are most numerous in the sulci of the brain, and may be seen around the nerve-roots. The inflammation sometimes spreads to the dura. The external surface of the brain is usually reddened, and small areas of softening are occasionally seen. The lining membrane of the ventricle may also be involved in the inflammatory process (**ependymitis**); the fluid is often greatly increased in the ventricles. In case suppuration does not occur the conditions are practically the same, with the exception that a serous or serofibrinous fluid, which may be slightly opaque, is present instead of pus. On microscopic examination the vessels of the meninges are found distended with blood, and the affected tissues are infiltrated with lymphoid cells and swollen connective-tissue cells; in the suppurative variety multitudes of polymorphonuclear leukocytes are also found. The sub-

jacent brain is usually infiltrated with polymorphonuclear leukocytes and lymphoid cells, and the nerve-fibers frequently show evidence of degenerative change, and are sometimes invaded by leukocytes. The same changes are found in the nerve-roots. Nerve degeneration, which will again be referred to, and more fully described, is evidenced in these situations by necrotic processes in the white substance and the formation of irregular masses or droplets, which may or may not be united to one another by thin filaments of myelin. A part of the white substance undergoes a fatty change.

Method for Demonstrating Nerve Degenerations.—This may be done by the myelin stains of Weigert, already referred to (p. 838). A better method is the following, which was devised by Marchi[1]:

Place the specimen in Müller''s fluid (p. 31), or the solution of Orth (p. 31), and allow it to remain eight days or longer. Remove, and cut into slices not more than three or four millimeters in thickness. Put these pieces into Marchi's mixture (p. 244); let the tissue remain in this solution for at least six or eight days. It is then removed, passed quickly through alcohol, and alcohol and ether, and is embedded in celloidin (p. 42). Examine the sections without staining. The fat in the degenerated nerves is stained black, while the normal nerves remain nearly colorless. This method depends on the fact that normal myelin, after remaining in Müller's solution eight or ten days, loses the property of being blackened by osmic acid, while any fat resulting from degeneration still retains this quality.

The term **meningismus**[2] has been applied to a condition in which the clinical symptoms all point to meningitis and the autopsy discloses no evidence of meningeal inflammation. In some of these cases bacteria which ordinarily give rise to inflammation are present. It is believed that the irritation produced by the bacterial toxins induces clinical phenomena without at the same time giving rise to exudates. The condition has been observed in typhoid fever, pneumonia, erysipelas, and in epidemic cerebrospinal meningitis. In some cases the microorganisms have been obtained by spinal puncture during life, and in other instances they have been demonstrated postmortem. Birnbaum calls this peculiar manifestation, meningeal sepsis without lesions.

In **tuberculous meningitis** the inflammatory phenomena vary with the number of tubercles and the resistance offered by the tissue to the development of the process. Occasionally, only a few small nodules are found—generally in the basal meninges or in the fissure of Sylvius. Under these circumstances there is no inflammation worth mentioning. In rare instances localized collections of such tubercles are present on the convexity of the brain, just in front of the fissure of Rolando; this variety of tuberculosis is called *meningitis en plaque.* Sometimes the tuberculous form is quite acute, and proves fatal in a few weeks; the exudate in these cases often possesses a peculiar jelly-like appearance. The inflammatory phenomena are, however, rarely so marked as in the suppurative forms; distinct tubercles are not formed, or, if so, they are

[1] For discussion for artefacts produced by the Marchi method see Stransky, "Neurolog. Centralbl.," July 16, 1903, p. 658. Meyer, "Centralbl. f. Nervenheil. u. Psych.," July, 1903, vol. 14, No. 7.

[2] Birnbaum, "Münch. med. Woch.," July 21, 1903. Staubi, "Deut. Arch. f. klin. Med.," vol. 82, Nos. 1 and 2.

very minute. On microscopic examination the appearance is much like that of nonsuppurative meningitis. There are, however, more marked changes in the small blood-vessels than are usually found in the ordinary inflammations. The adventitiæ, of the small arteries especially, are in a large degree replaced by lymphoid and plasma cells, and a like condition of the intimæ is frequently found. A peculiar change in some of the vessels is that their intimæ are pushed inward some distance from the muscular coats, and the space thus produced is filled with fluids and a few lymphoid cells. This condition has also been noted by Ohlmacher in meningitis due to the typhoid bacillus. The collections of cells around the blood-vessels are beginning tubercles, for bacilli may be detected within them, and occasionally a giant cell is seen. In chronic cases well-formed tubercles with caseous centers are encountered. If the inflammatory process encroaches on the nervous tissues beneath, more or less degeneration results, and the parts are infiltrated with lymphoid cells. Weill and Pehu[1] believe that tuberculous meningitis is never primary; of the sixty-eight cases which they studied at autopsy there was a notable adenopathy (tuberculous) in sixty-one, and in the other seven manifest tuberculous lesions in other parts of the body were present. In only ten cases did the viscera escape.

Syphilis of the Meninges.[2]—Gummata are sometimes found in the pia-arachnoid; they occur as flattened, pinkish or grayish nodules, which on section are often found to contain disintegrated tissue in which caseous material is frequently present. Around these nodules there is always a considerable increase in the amount of fibrous tissue, and the blood-vessels show evidence of obliterative endarteritis. A general and more acute syphilitic inflammation of the meninges of both the brain and cord is sometimes encountered. The appearance of the meninges is much the same as in the acute tuberculous form, and on microscopic examination but little difference is found in the histology of the two processes; however, evidence of obliterative endarteritis in the syphilitic form is usually present and the peculiar giant cells of tuberculosis are absent. Syphilis sometimes produces a chronic infantile meningitis, in which the membranes are opaque, thickened, and infiltrated with lymphoid cells.

Chronic alcoholic meningitis results, as the name indicates, from the prolonged and excessive indulgence in alcoholic beverages. The meninges of the cerebral convexities are chiefly affected. The process is never very marked. The meninges are slightly opaque and thickened, especially over the sulci, and along the sides of some of the vessels there may be streaks of lymph. The microscopic appearances are those of nonsuppurative meningitis, though the inflammatory phenomena are less marked. Chronic inflammatory conditions of the meninges may also result from the pressure of tumors, foreign bodies, etc.

[1] "Lyon Méd.," Aug. 9, 1903, p. 228. For discussion of the histologic changes of tuberculous meningitis see Diamond, "Trans. Chicago Path. Soc.," May 13, 1901. Also Armand-Delille, "Rôle des Poison du Bacille de Koch dans la Méningite Tuberculeuse et la Tuberculose des Centres Nerveux," Paris, 1904.

[2] Hirschl, "Wien. klin. Woch.," April 28, 1904, p. 465. Schaffer, "Neurolog. Centralbl.," Nov. 16, 1904, p. 1026.

Cerebrospinal meningitis[1] is an acute infectious disease, generally occurring in epidemics, and due to the Diplococcus intracellularis meningitidis (p. 111), also called the meningococcus. Although communicable, there has been considerable doubt as to the route by which infection occurred. It has generally been held that the meningeal lesion is due to hematogenous dissemination of the organism. The studies of Maragliano indicate that the meningococcus enters the cranial cavity from the nasal fossa. Mandoul and others have succeeded in cultivating an organism, believed to be the meningococcus, from the nasal mucus in cases of meningitis, and also in healthy individuals who have been in contact with possible sources of infection. Though not limited to any age, the disease is most frequent in individuals under twenty years, and is especially common during childhood and adolescence.

Morbid Anatomy.—In those cases in which death occurs within twenty-four hours the meninges are merely reddened; on microscopic examination a few lymphoid cells may be found in the vicinity of the vessels, and here and there small hemorrhages into the tissues are observed.

In the later stages the membranes are intensely injected, and are covered by purulent, seropurulent, and fibrinopurulent exudations. In more advanced

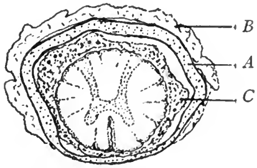


FIG. 408.—SPINAL CORD AND MENINGES.
Transverse section showing distribution of the exudates in meningitis.
A. Dura: *B*. Position of exudate in external pachymeningitis. *C*. Exudate in leptomeningitis.

FIG. 409.—PART OF SPINAL CORD AND MENINGES, DURA LAID OPEN ON POSTERIOR SURFACE; CASE OF EPIDEMIC CEREBROSPINAL MENINGITIS.
The cord and nerve-roots are covered by a thick seropurulent and fibrinous exudate, which, as the pia-arachnoid are more involved than the dura, is closely adherent to the cord.

[1] Councilman, Mallory and Wright, "A Report of the State Board of Health of Massachusetts," 1898. E. G. and Mary Hamilton Williams, "Jour. of Trop. Med.," 1900. Nuthall and Hunter, "Brit. Med. Jour.," Sept. 21, 1901. Jundell, "Nordiskt Med. Arkiv," Stockholm, 1901. Bettencourt and Franca, "Zeit. f. Hyg.," 1904, tome xlvi, p. 463. Rist and Paris, "Arch. Gen. de Méd. Exp.," 1904, No. 8, 449. Mandoul, "La Presse Méd.," Feb. 11, 1905, p. 89. Councilman, "Jour. Amer. Med. Assoc.," April 1, 1905. Maragliano, "Gaz. Osped. e delle Clin.," 1905, No. 19. See also Meningococcus, p. 111.

cases the membranes sometimes present the peculiar jelly-like appearance commonly observed in tuberculous meningitis; this is due to the exudate becoming more fibrinous in character. The lesions are most marked at the base of the brain and along the posterior portion of the cord; nevertheless, all parts may be affected. On the cerebral convexities there is usually more exudate in the vicinity of the fissure of Rolando than elsewhere. On microscopic examination the meninges are found greatly swollen, containing many multinuclear leukocytes and enlarged connective-tissue cells; fibrin is also present. The blood-vessels are often thrombosed; around some of the vessels a few lymphoid cells are occasionally present. Within the pus-cells many of the specific micro-organisms are found. Councilman recommends the following method for demonstrating them: Stain sections of tissues, which have been fixed in corrosive sublimate (p. 34) in a saturated solution of eosin (p. 50) in water, for an hour. Wash in water, stain one or two hours in Unna's alkaline methylene-blue (p. 48), diluted nine times with water. Wash with water. Dehydrate in absolute alcohol, clear in xylol, and mount in xylol-balsam. The bacteria and the nuclei are stained blue, while the tissues in general are reddish. In the chronic cases the exudation is much less in amount, being confined to small areas, and consisting of degenerated pus-cells and granular detritus. The chronicity of the process results in the meninges becoming much thickened, from the formation of new fibrous tissue. In this tissue lymphoid and plasma cells are found.

In the brain and cord the vessels are injected, and the substance of both of these viscera is somewhat softened and edematous. Punctiform hemorrhages are occasionally seen. Both the cranial and spinal nerves are swollen, reddened, and often infiltrated with leukocytes.

Microscopic examination of the brain and cord shows the blood-vessels engorged with blood; the endothelial cells are swollen and increased in number, and mitotic figures are frequently observed. The lesions in the brain-substance are generally not found below the molecular layer, though occasionally they extend much deeper—even entirely through the gray matter. The nervous tissues are more or less infiltrated with pus-cells, and the neuroglia cells become swollen and multiply. The ganglion cells are seen in all stages of degeneration, from slight irregularities in the chromophilic substance to its complete disappearance, and the final necrosis and disintegration of the entire cell, (Toluidin-blue or Nissl's method, see p. 837.) These changes are not so marked in the cord as in the brain. Many of the nerve-fibers in the brain, cord, and nerve-roots show degenerative changes, demonstrable by the methods of Marchi or Weigert. (See pp. 853, 838.)

Tumors of the Pia-arachnoid.—*Sarcomata*, either of the ordinary types or **endotheliomata**—especially the latter—are the most common of the new growths found in the meninges. They form round or flattened, soft, grayish or grayish-red tumors, which spread along the meninges and penetrate the brain-substance by means of the fibrous bands projected inward from the pia. Microscopically, they show the usual peculiarities of sarcoma or endothelioma. They occasionally occur as *angiosarcoma*, *myxosarcoma*, or *angiomyxosarcoma;* very rarely they are pigmented.

Rarer forms of tumors of the meninges are *myomata*, *fibromata*,

lipomata, *chondromata*, *osteomata*, and *teratomata*. Secondary sarcomata and epitheliomata may also occur. *Dermoid cysts* are sometimes found. Cysts produced by *echinococci* and *cysticerci* are sometimes encountered.

THE BRAIN.

Circulatory Disturbances.—Anemia of the brain occurs as a result of general anemia, whether the latter be symptomatic or essential. Any condition causing cerebral or meningeal edema lessens the amount of blood contained within the cranial cavity. Tumors and collections of fluid in the brain may also increase cerebral tension and proportionately lessen the blood-supply. When the blood-pressure suddenly falls, as in shock, fainting, and allied conditions, blood-distribution is altered and the brain receives less than its normal quantity. Cerebral anemia also results from the exhaustion following acute febrile diseases, and in this form is commonly due to cardiac weakness. Local cerebral anemia may be due to thrombosis, embolism, or obliterative disease of one or more arteries, and may be sufficient to cause atrophy or necrosis of the area supplied by the affected vessels. Tumors, cysts, meningeal hemorrhages, and inflammatory exudates that locally increase the pressure, proportionately diminish the amount of blood in the contiguous brain tissue upon which pressure is made.

Morbid Anatomy.—The only macroscopic evidence of general cerebral anemia is the pallor of the brain-substance. Microscopically, the smaller vessels contain but little blood; their walls may be thickened and hyaline. The ganglion cells often contain vacuoles, the tigroid substance stains indifferently or is fragmented (**tigrolysis**), and in advanced cases nuclear changes are present. In marked local anemia the structural alterations are commonly more intense and will be further discussed when considering softening.

Active hyperemia of the brain may be the result of over-action of the heart or of dilatation of the capillaries of the brain as a result of vasomotor disturbance; a sudden contraction of the arterioles of other parts of the body may also produce it. The hyperemia is local when a large branch of an artery becomes suddenly obstructed, thus causing more blood to flow through the neighboring branches. The brain is actively congested in the beginning of inflammatory conditions, such, for example, as arise from sunstroke; in the earlier stages of acute meningitis the blood-vessels of the brain-substance are usually intensely engorged.

Morbid Anatomy.—The brain usually exhibits more or less redness on examination, but attention should again be called to the fact that the presence or absence of unusual quantities of blood in the brain or its meninges is to be regarded as furnishing anything but reliable evidence as to the condition preceding death, as the position in which the cadaver has been allowed to remain affects very greatly the quantity of blood in any particular part. If, however, the hyperemia be due to inflammation, the area involved always shows some redness, especially if the condition be at all advanced. On microscopic examination the vessels are sometimes found distended with blood, and, if beginning inflammation be present, the usual evidences in the surrounding tissue will be apparent.

Passive hyperemia of the brain results from thrombosis of the larger venous sinuses, or pressure upon them by tumors, cysts, extravasations, and exudations; pressure on the superior vena cava or the innominate vein or thrombosis of these vessels, may also occasion it. Congestion of this type also occurs in those diseases of the heart causing distention of the venous system. It is also observed, to a limited extent, during violent muscular efforts, and is frequently marked when death has resulted from suffocation.

Morbid Anatomy.—The remarks made concerning the anatomic appearances in active hyperemia apply equally well to the condition under consideration. Microscopically, the veins are usually dilated, and they not infrequently rupture; in long-standing cases blood-pigment is sometimes present in the walls of the cerebral vessels. Edema of the brain may result from either variety of hyperemia, but always occurs if the passive form persists for any length of time. In this condition the arachnoid spaces are dilated.

General Pathology of the Ganglion Cells.[1]—Before considering those changes in the brain terminating in the formation of gross lesions of its substance it may be well to call attention to certain alterations in the ganglion cells that result from a large number of different morbific influences. These changes are, for the most part, of such a delicate character that they were not recognized by the older methods of research, and, hence, their very existence was not suspected until within the last few years. The exact nature of these changes is not clearly understood. They have been regarded as parenchymatous inflammations, occurring, as they somtimes do, simultaneously with inflammatory conditions of the surrounding tissue; but as they have been observed in a large number of conditions, clearly not inflammatory, it is very doubtful if they should be so considered. All these facts go to show that they are an invariable result of all influences, whatever their character, that act on the body in an injurious manner, and it would therefore seem much more logical to class them with the degenerations, or possibly beginning necroses. Moreover, there is nothing in the peculiar character of the changes that could stamp them as being of an inflammatory nature.

Among the most interesting of all the more delicate alterations that have been observed in ganglion cells are those described by Hodge as occurring in the ganglia and central nervous systems of animals as the result of long-continued electric stimulation, and also extreme fatigue. The following well-defined changes in the nerve-cells were observed: (1) *Nucleus:* Marked decrease in size. Change from smooth and rounded to a jagged irregular outline. Loss of open reticular appearance, with dark stains. (2) *Cell protoplasm:* Slight retraction in

[1] See Editorial, "Jour. Amer. Med. Assoc.," July 16, 1898, p. 131. Larkin and Jelliffe, "Med. Record," July 8, 1889. Ladams, "Nouvelle Iconographie de la Salpêtrière," 1900, Nos. 4, 5, and 6, p. 301. McCarthy, "Unv. of Penna. Med. Bull.," Jan., 1902. Turner, "Brain," Spring, 1903, p. 27. Ricketts and Rothstein, "Trans. Chicago Path. Soc.," Feb. 9, 1903, p 207. Hirshberg, "Maryland Med. Jour.," July, 1903, p. 257. Marinesco, "La Presse Méd.," Aug. 26, 1903. Spiller, "Jour. Med. Research," Aug., 1903, p. 142. Weisenburg, "Proc. Path. Soc. of Phila.," Feb., 1904, n. s., vol. vii, No. 3, p. 62. Bailey, "N. Y. Med. Jour.," July 16, 1904, p. 100. Odier, "Arch. de Méd. Exper.," July, 1904, p. 451. Laignel-Lavastine and Voisin, "Arch. Gen. de Méd. et Path. Anat.," March, 1904, p. 206. Weber, "Lubarsch and Ostertag's Ergebnisse der allg. Path. u. path. Anat.," Neunter Jahrg., I Ab., 1903, p. 212.

size with vacuolation for spinal ganglia; considerable shrinkage with enlargement of pericellular lymph-spaces for cells of cerebrum and cerebellum. Lessened power to stain or to reduce osmic acid. (3) For *cell-capsule*, when present: Decrease in size of nuclei. (4) Cells recover their normal condition if allowed to rest, but the process is slow. These changes would seem to have a bearing on those neurasthenic states following worry and long-continued and unremitting attention to the details of business.

More pronounced changes occur in the various intoxications, in the acute diseases, and accompanying the various brain affections. Berkeley has shown that more or less well-defined alterations are produced in the ganglion cells of the central nervous system of animals, and even more pronounced changes in the dendrites and gemmulæ of these cells, as the result of serum-poisoning and ricin-poisoning, and from the administration of alcohol.

Most marked changes in the chromophilic substance (toluidin-blue method) of the nerve-cells have been observed in a large number of different conditions in man, such as acute alcoholism, sunstroke, eclampsia, diabetes, uremic conditions, the anemias, all the infectious diseases, and in the auto-intoxications.

The change most frequently observed is fragmentation of the chromophilic masses of the cells (**tigrolysis**), giving them the appearance of being smaller and more numerous than usual; if the disease-producing cause be severe, or if it continues to act, these bodies partly or completely disappear. In rare instances the bodies unite with each other, forming collections of chromophilic substance much larger than normal; all the tigroid may unite, in which case the entire cell is stained almost uniformly. In all these conditions the quantity of pigment around the nucleus, if it existed primarily, may be greatly increased, or, if none is present, considerable quantities may form. The peculiarities of these pigment particles were referred to in describing the histology of ganglion cells. (See p. 837.) When the degeneration is pronounced, the nuclei manifest a tendency to pass from the center of the cell to its periphery, and it has even been asserted that they may be partly or completely extruded from the protoplasm. Simultaneously, the nuclei often show a tendency to mitotic division, or they swell, and several vacuoles appear within a single nucleus; and finally the nuclear outlines become indistinct or disappear, the nucleolus is no longer visible, the scanty chromatin fragments (**chromatolysis**), the cell disintegrates (a form of **cytolysis**), and at last disappears, often a prey of phagocytic leukocytes.

In sections stained by the toluidin-blue method (p. 837) the processes and axis-cylinders of cells in severely diseased areas often appear broken off, giving the cell a smooth, rounded contour.

Changes in the Dendrites, Gemmulæ, and Neurofibrils.—Unfortunately the method of Golgi (p. 836) does not yield sufficiently constant results to be trustworthy in studying the degenerative and necrotic changes affecting such appendages of the ganglion cell as the dendrites, gemmulæ, and cylinder processes. So far, however, as these studies have been extended they show that the structures mentioned participate in the alterations occurring in the body of the cell. The protoplasmic processes are often varicose, the gemmulæ scanty or absent, and some-

times fragmented. The neurofibril impregnation methods (p. 838) offer sufficiently constant results to be of value in identifying the nature of finer changes[1] occurring in the ganglion cells and their processes. Marinesco has been able to confirm Cajal's observation that in tetanus and rabies the intracellular fibrils are often swollen or fragmented and in advanced cases are no longer demonstrable. In infectious diseases and other conditions in which changes occur in the tigroid substance of Nissl, analogous alterations are found in the fibrils. In various forms of insanity the neurofibrils are altered, although Dagonet has shown that in general paralysis many of the fibrils persist. Ludlam's studies establish that in mental disease irregular granularity and fragmentation of the intracellular fibrils constantly occur. Under the name **neuronophagia** has been described a condition characterized by accumulations of cells, leukocytic or neuroglia, which encroaches upon and replaces the ganglion cells. Such accumulations have been noted particularly in **rabies,** and were thought by some to be pathognomonic of that disease. In this affection the changes seen, especially in the intervetebral ganglia, consist of atrophy of the nerve-cells, and proliferation of the capsular endothelium, giving rise to round cells that eventually fill the space previously occupied by the ganglion cell. In addition to the pericellular infiltration the vessels of the central nervous system are usually found distended, mononuclear cell elements accumulate around the numerous ganglion cells, forming small masses which have been designated "rabic tubercles." With regard to the etiology of rabies[2] we are still in doubt, although the infectious nature of the disease has been clearly established; Negri described an organism, thought to be of a protozoan nature, which is generally accepted as the cause.

It should not be forgotten that in bodies that have undergone postmortem change the nerve-cells exhibit alterations closely resembling those produced by disease. But at ordinary temperatures abnormal conditions will not be, as a rule, at all marked during the first twenty-four hours following death; if the body be frozen, changes may not occur even after many days. The alterations consist in a swelling of the cells, followed by the gradual loss in staining power of the chromophilic (tigroid) bodies and the appearance in the protoplasm of large vacuoles; the protoplasmic processes often fragment and the cell assumes an irregular outline. The nucleus swells also, and its outlines become blurred, and it may be dislodged and pass to one end of the cell; at a later period it entirely disappears. The nucleolus, last of all, swells, disintegrates, loses in tingibility, and finally disappears.

Secondary Degeneration of Fibers.[3]—Over a half century ago Waller

[1] Marchand, "C. R. Soc. Biol.," 1904, tome 57, p. 251. Dagonet, "C. R. Soc. Biol.," 1904, tome 57, p. 298. Marinesco, "C. R. Soc. Biol.," 1904, tome 57, p. 407, July 9, 1904, p. 62, and March 25, 1905; also "Revue Neurolog.," May 15, 1904, p. 405, and Aug. 15, 1904, p. 813. Bayon, "Centralbl. f. allg. Path. u. path. Anat.," 1905, Bd. xvi. Ludlam, "Jour. of Nerv. and Mental Disease," Jan., 1905.

[2] For a review of the literature of rabies see Remlinger, "Bulle. de l'Inst. Pasteur," 1904, tome ii, pp. 753 and 793. Also Ravenel and McCarthy, "Proceed. of Path. Soc. of Phila.," 1901, n. s., vol. iv, No. 5, p. 89. Negri, "Zeit. f. Hyg. u. Inf.," vol. xliii, No. 3. Buhlig, "Amer. Med.," Nov. 26, 1904. Luzzani, "Arch. per le Sci. Méd.," 1904, vol. xxviii, No. 11. Konradi, "Centralbl. f. Bakt.," Feb. 18, 1905, p. 194. Maas, "Münch. med. Woch.," 1905, No. 3, p. 119.

[3] Halliburton, "Lancet," June 22, 1901. Ballance and Stewart, "The Healing

demonstrated that if a nerve be divided, the part distal to the cell from which the fiber receives its impulses, degenerates; this process is called **Wallerian degeneration** and is of the greatest importance in the study and comprehension of degenerative lesions affecting the fibers of the central and peripheral nervous system. If the cells in the motor cortex be destroyed, a tract degeneration follows the course of the fiber through the internal capsule, medulla, and cord. If the fibers within the internal capsule are destroyed by injury, hemorrhage, softening, or neoplasm, those coming from cortical cells degenerate down to the motor cell in the cord with which they communicate; a transverse section of the cord gives rise to an ascending degeneration of nerve-fibers belonging to ganglion cells lying below the lesion and descending degeneration develops in the fibers coming from above the injury. Pressure of a sufficient degree produces similar changes. If a peripheral nerve be sectioned, bruised, or infiltrated by a tumor, the distal portion degenerates. In addition to the degeneration occurring in a fiber beyond the primary lesion, there is also a proximal degeneration which, in the peripheral nerves, extends to the first node of Ranvier; there are also slight changes in the tigroid substance of the cell with which it communicates, but these alterations are inconspicuous, appear late, and are far less important than the degeneration distal to the point of injury.

The rapidity with which Wallerian degeneration occurs is largely dependent upon the suddenness of the disturbance that separates the peripheral from the proximal parts. When tumors infiltrate or press upon the fiber, its conductivity gradually disappears. When, however, it is sectioned, torn apart, or in other ways suddenly injured, the changes follow a fairly definite order. The studies of Halliburton, Ballance and Stewart, and others show that for the first three days following the injury the distal part of the nerve remains irritable and competent to transmit impulses. From the fourth to the sixth day the irritability progressively diminishes, and, by the end of this time, fragmentation of the myelin becomes marked. From the sixth to the eighth day fatty changes can first be demonstrated by the Marchi method (p. 853), and this microchemic reaction persists for from twenty-five to thirty-five days. The fragmenting myelin, as a result of necrotic and degenerative changes, undergoes disintegration, and is removed largely through the intervention of phagocytic cells, in which particles of this substance may occasionally be demonstrated as long as the fifth month after the reception of the injury. Regenerative processes may be inaugurated as early as the end of the second week; these will be further discussed in considering repair of nerves at the close of this chapter.

Intracranial Hemorrhage.—Hemorrhage within the skull cavity may be in the membranes, in which case it is known as meningeal hemorrhage, or in the brain-substance (cerebral hemorrhage). Meningeal hemorrhage may again be divided according to its location: (1) *Extradural*

of Nerves," 1901. Bowlby, "Lancet," July 26, 1902. Oberthur and Monseaux, "Rev. Neurolog.," Aug. 31, 1902, p. 812. Moyer, "Jour. Amer. Med. Assoc.," Oct. 25, 1902, p. 1043. Henriksen, "Lancet," April 11, 1903, p. 1015. Spiller and Frazier, "Univ. of Penna. Med. Bull.," June, 1903. Cattwinkel and Kerschensteiner, "Lubarsch and Ostertag's Ergebnisse der allg. Path. u. path. Anat.," Neunter Jahrg., I Ab., 1903, p. 9. Mott, Halliburton and Edmonds, "Proceed. of Physiological Soc.," March 19, 1904. Kennedy, "Brit. Med. Jour.," Sept. 24, 1904, p. 729.

hemorrhage is between the dura and the skull; when the hemorrhage is within the dura mater separating that membrane into layers, it is called (2) *intradural hemorrhage;* when the extravasated blood is beneath the dura, the condition is spoken of as (3) *subdural hemorrhage.* Such hemorrhages are practically always due to injury with or without fracture of the cranial bones. In hemorrhagic pachymeningitis (see p. 849) the hemorrhage is rarely profuse. The extended blood may, by pressure, influence the cerebral cortex, giving rise to degenerative and necrotic processes, and finally softening. It may undergo organization, either complete or partial, and persist in the form of cicatricial tissue. The most important form of intracranial hemorrhage is that occurring within the brain-substance.

Cerebral hemorrhage includes all forms of hemorrhage into the brain tissue or the ventricles.

Etiology.—The most common form of cerebral hemorrhage is that occuring in individuals who are almost always over forty years of age, and is due to arteriosclerosis affecting the smaller arteries in the brain, causing minute aneurysms, which subsequently rupture; this constitutes one form of the clinical condition called **apoplexy.** (See Arteriosclerosis, p. 525.) The affection just named is usually characterized by a sudden loss of consciousness and varying degrees of paralysis, and may be due to hemorrhage within or upon the brain or to embolic plugging or thrombosis giving rise to acute cerebral softening. The form due to hemorrhage from the meninges, sometimes called **meningeal apoplexy,** is, by most writers, distinguished from types depending upon intracerebral lesions. When due to embolism or thrombosis, it is called **embolic** or **thrombotic apoplexy**; and when produced by hemorrhage within the brain, **hemorrhagic apoplexy.** Hemorrhage either from the meninges or brain-substance may result from violence, and may, of course, occur at any age. In addition to these causes, small punctiform hemorrhages into the brain are occasionally observed in syphilis, purpura, scurvy, and leukemia, and in interstitial nephritis; such hemorrhages are also found, as has been before mentioned, in meningitis and in hyperemia of the brain. Arteriosclerosis (p. 525), and any form of vessel degeneration (p. 520) in which the vascular wall is weakened, are most frequent causes. Infective endocarditis, or other morbid process attended by the presence of bacteria in the circulation, sometimes causes infection of the vessel wall, as a consequence of which rupture and hemorrhage occur. It is therefore possible for embolic processes to cause apoplexy by embolism or as a result of hemorrhage. The lesion resulting from bacterial softening of the vessel wall is called **mycotic aneurysm.**[1] Lastly, hemorrhage sometimes occurs from small vascular tumors.

Morbid Anatomy.—In that variety produced by disease of the blood-vessels the hemorrhage is nearly always solitary. According to Charcot and Bouchard, disease of the blood-vessels of the different parts of the brain occurs in the following order as regards frequency: Central ganglia, cortex, pons, cerebellum, centrum ovale, middle cerebellar peduncle, crus cerebri, and medulla oblongata; as might be expected, this order corresponds closely to the incidence of hemorrhage. The most

[1] Simmonds, "Centralbl. f. Chir.," Leipzig, May 18, 1901, and "Deut. med. Woch.," May 30, 1901. See also p. 284.

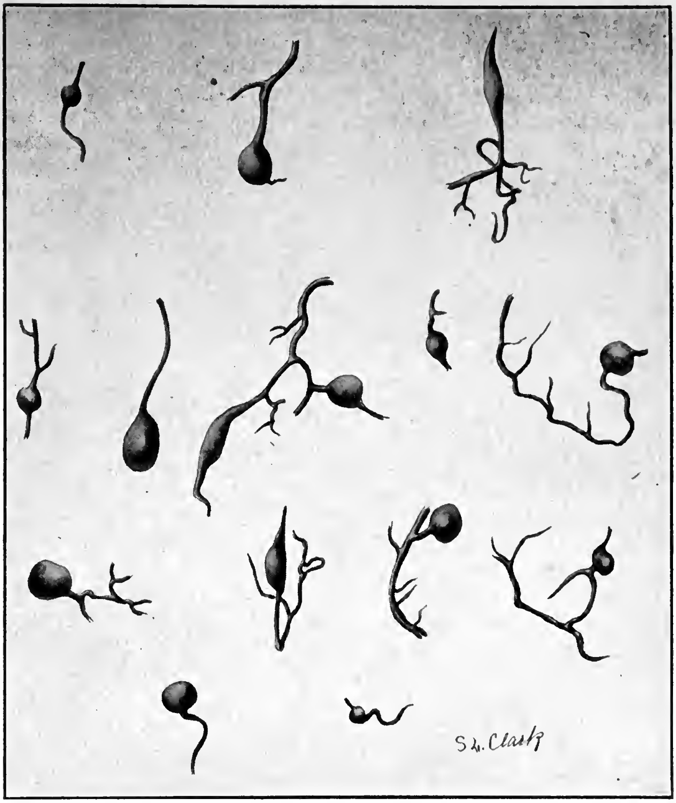


FIG. 1.

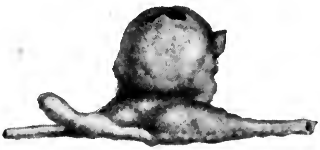


FIG. 2.

MILIARY ANEURYSMS.

(From cases of hemorrhagic apoplexy By permission Dr. Ellis, "International Clinics.")

FIG. 1.—Aneurysms assembled from several brains. (Natural size.)

FIG. 2.—Vessel bearing a ruptured aneurysm. (Twice natural size.)

frequent seat, however, is the internal capsule; this is explained by the fact that the small vertical arteries which are distributed to this part, namely, the lenticulostriate and lenticulothalamia, have no collateral branches, are under a high pressure, and are often diseased; these arteries frequently contain miliary aneurysms (Plate XXIII). One side of the brain is affected as often as the other. Though very rare, the hemorrhage occasionally occurs directly into the ventricles from the choroid plexuses, but the blood quite frequently finds its way into the ventricles by bursting through from the ganglia that form part of their walls. On cutting into an area of hemorrhage there is found toward the center a mass of clotted or semiclotted blood, merging on every side into the surrounding torn and lacerated tissues, which are often infiltrated with blood for some distance beyond the center of the lesion, thus giving the appearance of separate and distinct hemorrhagic areas in the vicinity. In rare instances almost the entire hemisphere into which the hemorrhage occurs is destroyed. In the immediate area of the hemorrhage the nervous substance is, of course, entirely destroyed, and on microscopic examination contains only the debris resulting from the disruption of the normal structures of the part. If the patient does not succumb to the immediate attack, the extravasated blood begins quickly to undergo changes; it shrinks, and the color gradually fades until finally it is of a reddish-yellow hue. In the mean time the presence of the blood in the tissue results in an inflammatory condition of the neighboring structures, and in the formation of a fibrous capsule around the clot. In some cases a capsule is not produced, for the reason that some of the pyogenic organisms gain entrance to the part, and suppuration results; the condition then really becomes one of abscess. As the capsule forms around the extravasated blood, it gradually becomes smaller, as the result of absorption, but the newly formed fibrous tissue remains as a scar. In some instances the blood-clot undergoes liquefaction, and, becoming encapsulated, remains as a cyst; it is thought that the fluid contained within such cavities is sometimes absorbed, and that they may be replaced by fibrous tissue. As a result of the formation and subsequent contraction of scar tissue, the area in which the hemorrhage occurs is often markedly reduced in size. While the quantity of newly formed fibrous tissue depends on the extent of the hemorrhage, the fact should be carefully noted that it is not merely equivalent to the amount of nerve tissue destroyed primarily, but that it also represents the sclerosis consecutive to the secondary degeneration in the nerve-fibers, the ganglion cells of which have been destroyed, or the courses of which have been interrupted by the lesion. The character and extent of these secondary degenerations (p. 860) depend, of course, entirely on the situation of the hemorrhage; should sensory fibers be damaged, the secondary degeneration is toward the nerve-centers, while injury to the motor fibers causes degeneration from the nerve-centers toward the periphery of the body. These degenerations may be detected by the method of Marchi (p. 853) as early as the eighth or ninth day following the hemorrhage; at a later period, the fat having disappeared largely, the changes are best shown by Weigert's method. Later, compound granule bodies and corpora amylacea appear in the situations where the degenerative process is going on; the neuroglia increases, and, in the course of time, a mass of scar tissue replaces the degenerated area. If the brain-substance be carefully

washed from the smaller arteries, minute saccular dilatations, which are really false aneurysms, will be disclosed. These aneurysms are the result of an arteriosclerotic weakening (see p. 525) of the vessels, which subsequently causes a partial rupture and overdistention of the remaining coats. It is the final complete rupture of such a vessel, the wall of which is weakened, that causes the hemorrhage. Charcot believed that a special form of periarteritis induced this vascular change now known to be of arteriosclerotic origin.

Concerning the hemorrhages resulting from injury, or those occurring in connection with tumors and general diseases, there is nothing of importance to be said in addition to the remarks on hemorrhage from diseased blood-vessels. It may, however, be observed that the hemorrhages are often multiple, and are, as a rule, smaller than those produced in the usual way.

Infantile meningeal hemorrhage may be classed with those conditions in which hemorrhage occurs directly into the brain-substance, for, although it is, strictly speaking, a result of injury to the meningeal vessels, the effect is to cause compression of the brain-substance and to produce symptoms that correspond. The blood is effused over the convex surface of the brain or along the base; the former is said to be more common in foot presentation and the latter in head presentation; the condition rarely follows normal labor.

Occlusion of the vessels of the brain gives rise to a process in its substance commonly called **cerebral softening.** The most common causes of softening are thrombosis, embolism, and arteriosclerosis of the cerebral vessels, but, in addition to these, it may result from inflammations of the brain-substance, and occasionally occurs in old age without assignable cause. Thrombosis of the cerebral vessels is due most commonly to obliterative endarteritis and atheroma; as the former of these conditions is probably always syphilitic, and the latter frequently so, it is evident that syphilis plays an important rôle in the production of this condition. A vessel may also be occluded by pressure of tumors, masses of cicatricial tissue, and cysts. In peculiar states of blood accompanying child-birth, in acute diseases, and in cancer, gout, tuberculosis, and general malnutrition, marasmic thrombi (p. 273) are sometimes formed. Embolism results most commonly from diseases of the endocardium or its valves, but may arise from diseased conditions of the aorta or other large vessels; the plug sometimes comes from the lung, and may have originated in an aneurysm or morbid growth. (See Embolism, p. 278.)

Morbid Anatomy.—When one of the cerebral vessels is occluded, the collateral circulation is rarely sufficient to cause anything like complete compensation; in the vast majority of instances the blood is practically excluded from the area supplied by the vessel involved, and, as a result, the tissue in the situation quickly dies. Thrombosis from syphilitic disease occurs more commonly in the larger vessels. Embolism of the middle cerebral arteries and their branches is more common than in the other vessels, and the vessels of the left side are more frequently plugged than those on the right. The immediate effect of the obstruction of a vessel, either as the result of thrombosis or embolism, is the arrest of the blood-supply to the region supplied. As a result of interference with blood ingress, the area involved appears abnormally white; after twenty-four or thirty-six hours serum begins to collect in

the part, pushing the nerve elements apart and rendering the tissue edematous; as a result of increased permeability and rupture the blood escapes from the affected vessels and the region involved assumes a yellowish or reddish color, depending on the quantity of blood effused. The nerve elements rapidly undergo degenerative and necrotic changes, and disintegrate, forming a mass of granular detritus; by the time this stage is reached the so-called *compound granule cells* become exceedingly numerous. These bodies are probably leukocytes exerting their usual phagocytic properties. The granular matter contained within the protoplasm of such cells is derived from the necrotic erythrocytes and tissue elements; they also contain a small quantity of fat. The change so far observed is essentially the same as that occurring in other forms of infarction, modified somewhat by the peculiar chemic composition and architecture of the cerebral tissue; it is essentially a necrosis. In the course of a few weeks the blood-pigment from the degenerated red cells begins to be absorbed, and as this process advances, the area, at first more or less of a reddish color, becomes yellowish, and finally white. These stages correspond to the **red, yellow,** and **white softening** described by various authors. Red softening is most marked in the cortex, where the blood-vessels are numerous; yellow softening results from the red by degenerative changes in the blood-pigment and by its absorption. White softening, in its purest form, generally occurs only in the white substance of the hemispheres. The area involved may be swollen and softer than the surrounding normal tissue; oftentimes it differs but little from the contiguous healthy substance.

In the early stages inflammatory reaction on the part of the surrounding tissue is evidenced by an increase of the neuroglia cells, and the migration of a few leukocytes from the normal blood-vessels in the vicinity. In white softening particles from the diseased region show, when examined under the microscope, a *granular dertitus*, *nuclei from the neuroglia*, *compound granule bodies*, and, at a late stage, *corpora amylacea*. The changes produced in the nerve-fiberspassing through the diseased area are the same as those following hemorrhage.

If the softened areas are infected by any of the putrefactive or pyogenic bacteria, changes are induced that correspond to the peculiar micro-organism present. If the results of the occlusion do not earlier prove fatal, in the course of a few months or years the affected area may become encapsulated, and, if the contents be absorbed, a dense mass of fibrous or gliomatous tissue entirely replaces it. It sometimes happens that the solid parts alone are absorbed from the softened tissue, and a cyst results.

An examination of the vessels of a brain in which thrombosis has occurred usually reveals the presence of an obliterative endarteritis or atheroma or other evidence of vascular disease. In the first-named condition the vessels exhibit hard, nodular swellings along their course, which are the result of an increase in the thickness of their walls, and are never aneurysmal in character. The microscopic changes consist of a great increase in the amount of fibrous tissue in the inner coat of the vessels, and an alteration of the same character may be present in the outer tunic. The intimæ so thicken that the lumina of the vessels are greatly reduced in size. At the point where the obstruction producing the softening has occurred, the decrease in caliber of the vessel is so great that a thrombus has been produced.

In case the vessels are atheromatous there will be found some thickening of the inner coats, and subsequent fatty degeneration with the possible formation of ulcers or calcareous plates resembling those often found in other vessels so diseased (p. 520). The obliterative change results in this case by the building up of a fibrinous plug from an ulcer, or the formation of like obstructions from the narrowing of the lumina of the affected vessels.

Thrombosis of the veins and sinuses is sometimes encountered; it may result from an altered condition of the circulating blood or from morbid processes primary in the vicinity of the vessels. Among the former are the blood states resulting from long-continued diarrhea, suppuration of any kind, acute infections, and diseases of the lung; it also occurs in the puerperal state and during the course of cancer. The condition is especially frequent in children. Belonging to the class of abnormal conditions that produce thrombosis by their proximity to the veins or sinuses, are injury or diseases of the bones of the skull, internal ear diseases, meningitis, tumors, erysipelas, carbuncle, and the presence of foreign bodies.

Morbid Anatomy.—In the great majority of instances the clot is situated in the superior longitudinal sinus; this is probably in a measure due to the fact that the veins empty into it in a forward direction, and the current of the entering blood is therefore opposed to the course of that of the blood in the sinus, and, as a consequence, its circulation is feeble. The obstruction causes intense congestion in the blood-vessels supplying the occluded sinus, and edema in the area involved; this congested condition of the vessels may lead to rupture of the smaller veins, so that many minute areas of hemorrhage are often observed. Softening of the cerebral tissues occurs in the vicinity of the edematous and hemorrhagic spots. Within the vessels involved there may be found a clot, limited to one part or occupying its entire extent, at first dark and soft, but later becoming harder and more or less laminated, as a result of the deposition of successive layers of fibrin.

Infantile hemiplegia is a condition the pathology of which is not clearly established, although there is considerable evidence indicating that it is the result of vascular obstruction. It occurs in children, following the acute infectious diseases. In connection with paralysis in infancy there is an important congenital condition which deserves special mention. According to Flechsig, the fibers of the pyramidal tract possess no myelin at birth and the axis-cylinders begin to make their appearance at the end of the fifth month. In prematurely born children the pyramidal (motor) tract is, therefore, not developed (**agenesis**). For this reason children born before term, especially at six or seven months, frequently present a spasmodic state of the limbs which may be permanent. The condition is called **diplegia.**

Inflammations of the brain (**cerebritis, encephalitis**), like inflammations elsewhere, may be acute or chronic; in addition, they may be simple, hemorrhagic, purulent, or productive.

Acute Inflammations.—The classification of acute inflammations of the brain is at the present time, unfortunately, in a state of great confusion. Authorities generally recognize the following varieties: (1) **Acute encephalitis,** the result of injury[1]; (2) **simple acute focal ence-**

[1] Rawling, "Lancet," 1904, vol. i.

phalitis (hematogenous or insular), the result of the acute infectious diseases; (3) **acute hemorrhagic encephalitis**; (4) **acute suppurative encephalitis.**

It is obvious that at the time an injury occurs there is always a strong probability that the wound will become infected with some micro-organism, and to the results of the injury *per se* there will be quickly added the effects resulting from the presence of the particular infectious agent introduced, and every feature of the process is accordingly modified; again, nothing can be more inaccurate than merely to say an encephalitis occurs during some infectious or septic process, since the peculiarities of the condition induced must vary as widely as the diseases from which they take their origin. Even the term suppurative encephalitis is wholly unscientific, as there are many infectious agents capable of setting up a process of this kind. As much as this condition of affairs is to be deplored, in the present state of our knowledge we can perhaps do no better than to follow the classification just referred to, with the exception only that all those inflammations of a suppurative character, including abscess, will be included under one head.

The peculiarities of an inflammation the result of injury will, of course, depend on the situation, kind, and extent of the wound. If no infective agent be added, the changes resemble the alterations following hemorrhage. The nerve substance in the vicinity of the injury is destroyed, and there is more or less inflammatory infiltration of cells into the part. A fibrous or gliomatous wall may ultimately form around the diseased area. The subsequent changes in the softened tissue and the secondary degenerations ensuing are identical with those that follow hemorrhage.

Simple acute focal encephalitis[1] is a condition in which the exciting cause of the inflammation probably always reaches the brain by means of the circulation. It may occur in connection with any of the infectious diseases, such as influenza, typhoid fever, diphtheria, and rabies; it sometimes results from rheumatism, and may follow sunstroke.

Etiology.—In some cases the lesion is due to the same micro-organism that gives rise to the disease in connection with which it occurs, and in other instances the general condition acts as a predisposing cause, producing such a lowered state of resistance on the part of the tissues of the brain that other infectious agents happening to gain entrance to the part, find no difficulty in lodging and in producing the peculiar lesions which they occasion. It is not impossible, also, that the soluble poisons that are manufactured in the body in some infectious diseases may act directly as irritants to the brain tissues.

Morbid Anatomy.—The lesions are generally scattered throughout the brain-substance as small foci, which may or may not be macroscopically perceptible. When large enough to be seen, they generally present a red appearance, and are softer than the neighboring cerebral tissue. The areas are usually considerably redder than those of simple softening, this being due to the dilatation of the vessels in and around the diseased region, and to more or less extravasation of blood into the part. For the foregoing reasons inflammation of the brain was long confounded with

[1] Bauchs, "Neurolog. Centralbl.," Feb. 1, 1903, p. 109. Brooks, "Med News," Aug. 8, 1903, p. 241. Bullard and Sims, "Boston Med. and Surg. Jour.," Dec 15, 1904.

softening, with which it presents many points in common. At a later stage, indeed, it may be impossible to distinguish between them, for the extravasated blood is gradually absorbed, or its coloring-matter so modified that the area becomes pale. During the period of acute inflammation sections, when examined microscopically. show distention of the blood-vessels, small focal hemorrhages, and accumulations of lymphoid cells around the vessels. At a later stage there are many larger cells that appear to be derived from the connective tissue or neuroglia; there are also many plasma cells. The nerve-cells and nerve-fibers manifest necrotic and degenerative changes. If the area be small, it is not improbable that practical restitution to its normal condition may occur; but if larger, the most favorable result that can be anticipated is the formation of a cyst or a small scar, which replaces the tissue involved. Adhesions of the meninges to the cortex are frequently found.

Acute hemorrhagic cerebritis[1] is a rare affection probably due to a number of causes, although in many cases the etiology can not be determined. Twenty years ago Leichtenstern suggested that the process was of infective origin, and succeeding observations have strengthened this view. Considerable doubt is entertained as to whether there is any essential difference between the acute simple or focal encephalitis and the lesion at present under discussion; the presence or absence of hemorrhage depends upon a number of factors, and it is not improbable that the same causes may induce either form. A number of bacteria have been identified in lesions of acute hemorrhagic cerebritis; Southard and Keene have induced similar changes in guinea-pigs by experimental inoculation with the Staphylococcus pyogenes aureus. Hoppe believes that it frequently follows measles, and less commonly typhoid, scarlet fever, diphtheria, and influenza; trauma is also a cause. In some cases both brain and spinal cord are involved—**encephalomyelitis hæmorrhagica.** There is an intimate relation between the condition and cerebral softening, although in the latter the lesions are much larger. The centrum ovale is said to be the part of the brain principally involved; it is locally or diffusely softened, of a pinkish color, and contains numerous minute hemorrhages. The pia is also injected. The blood-vessels of the white substance are seen to be distended with blood when examined microscopically, and there are slight evidences of degeneration of the nerve-fibers in this situation. Hemorrhagic foci are frequent, areas of leukocyte accumulation numerous and generally small. The nerve-cells of the cortex are normal, or but slightly changed; the alterations in these bodies are those usually accompanying infections and possess nothing peculiar to this affection.

Polioencephalitis is an acute inflammatory condition affecting the motor nuclei of the brain; when the centers for the third, fourth, and sixth nerves are involved, the condition is called **polioencephalitis superior**; when the nuclei of the seventh to the twelfth nerves, inclusive, are affected, the term **polioencephalitis inferior** is applied; in some instances the anterior cornua of the cord are also affected, justifying the name **polioencephalomyelitis.** The ganglion cells of the affected area

[1] Hoppe, "Jour. of Nerv. and Ment. Dis.," Sept., 1902, p. 524. Strāussler, "Jahrb. f. Psychiat. u. Neurolog.," 1902, vol. xxi, p. 253. Hinsmans, "Berl. klin. Woch.," Jan. 23, 1905. Southard and Keene, "Amer. Jour. of Med. Sci.," March, 1905, p. 474.

are swollen, the tigroid and nuclear stainable substances are altered, the axones and dendrites swollen and fragmented, and leukocytic accumulation in the contiguous tissue sometimes marked; hemorrhages also may be present. When affecting the nuclei of the bulb, this condition constitutes the anatomic basis of **acute bulbar paralysis.** If the patient survive, sclerosis probably follows.

Suppurative Cerebritis.[1]—By far the most frequent and important of all the inflammatory conditions affecting the brain are those of a suppurative character. The disease may occur as a complication of any acute infective process, such as erysipelas, pneumonia, cerebrospinal meningitis, typhoid, scarlet fever, and even influenza. It is frequently observed in conditions accompanied by the presence of pyogenic cocci in the circulating media of the body. Metastatic cerebral abscesses occur in pyemia, septicemia, endocarditis, phlebitis, with or without throm-

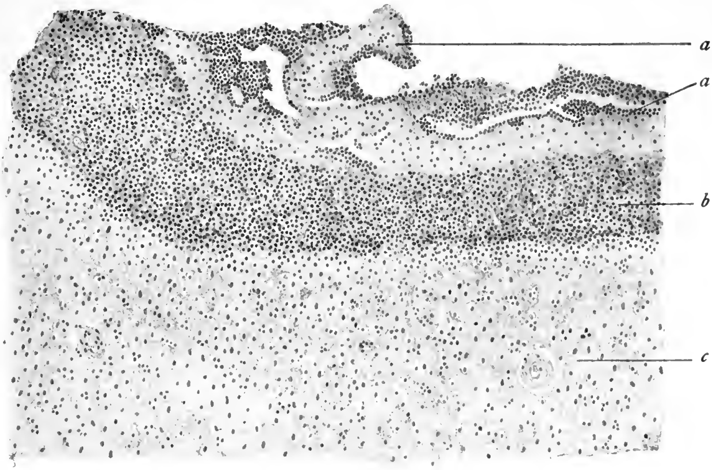


FIG. 410.—SECTION OF HUMAN BRAIN INCLUDING WALL OF CEREBRAL ABSCESS.
a, a. Periphery of abscess; necrotic tissue containing pus-cells and granular detritus. *b.* Wall containing reparative elements. *c.* More or less normal brain-substance. (Queen obj., ⅙-inch; oc., B.)

bosis, and suppurations of distant parts. But at the present time more common than any of these causes is the direct or indirect extension of suppurating processes to the brain-substance from neighboring structures, such as occurs in middle-ear disease, chronic diseases of the nose, caries of the bones of the skull, and suppurative lesions of the meninges. The most frequent cause is a suppurative process affecting the middle ear or mastoid. Ehrnrooth has shown experimentally that blows on the head increase the susceptibility of the cerebral tissues to infection by bacteria circulating in the blood.

The most frequent organisms present in these conditions are the Streptococcus pyogenes, the Staphylococci pyogenes albus, aureus, and

[1] Clayton, "Phila. Med. Jour.," March 2, 1901. Ehrnrooth, "Arbeit. a. d Path. Inst. Helsingsfors," 1902, Abth. I, p. 101. Hoppe, "Jour Amer. Med. Assoc.," March 14, 1903, p. 702. Kolpin, "Deut. Zeit. f. Nervenheilk.," 1904. Bd 25, p. 465. Fauvel, Thèse de Paris, 1904, No. 189.

citreus, pneumococcus and the Bacillus pyocyaneus; actinomyces are also occasionally observed; the oidium albicans has been found, and other organisms are sometimes the cause.

Morbid Anatomy.—When the organisms producing the disease enter the brain by means of the circulation, numerous minute foci of inflammation usually occur; macroscopically, these resemble in every way the areas found in the simple acute form of cerebritis. When the infection comes from neighboring structures, it generally extends by continuity of surface to one part of the brain alone, and there occurs, as a consequence, a localized inflammation at the infected point only. When the diseased area is extensive, it is commonly called, when situated in the cerebrum, **cerebral abscess,** and, when the cerebellum is affected, **cerebellar abscess.** The cerebrum is involved about four times as frequently as all the other parts together; next to the cerebrum the cerebellum is most frequently affected. The typic brain abscess usually contains a collection of yellowish or greenish, often fetid, pus, which, in addition to polymorphonuclear leukocytes, is loaded with the granular debris resulting from necrosis and disintegration of the nervous structure; in acute cases bacteria are present in large numbers; when the abscess has persisted for some time, microorganisms are often scanty or even absent. The walls of the abscesses are irregular; often there are several abscesses near one another, connected by small sinuses. The surrounding tissue is swollen and pinkish in color; if the abscess be old, it is not infrequently surrounded by a more or less well-defined capsule of fibrous tissue.

Microscopically, the walls of the abscesses show degenerating nerve-cells and nerve-fibers, an increase in the neuroglia cells, and infiltrating these areas of necrotic and disintegrating tissue are multitudes of polymorphonuclear leukocytes (pus-cells), which have migrated from the surrounding engorged blood-vessels; enlarged connective-tissue cells, lymphocytes, and, especially if the process be subacute or chronic, numerous plasma cells are also found. The capsules of very old abscesses sometimes undergo calcareous change, and, in rare instances, the contents may be similarly affected.

Chronic Encephalitis.—But little is known of the chronic inflammatory conditions affecting the brain-substance alone, such lesions being apparently very rare. It is, however, quite conceivable—and even probable—that acute inflammatory processes, especially those of a nonsuppurative character, may in some instances become subacute or chronic. Cases have been recorded in which there was postmortem evidence of such conditions, but it was impossible to say whether the cerebritis began as a chronic process or followed an acute inflammation. The macroscopic changes are slight or wanting in chronic cerebral inflammations; microscopically evidences of slight inflammation, and sometimes small areas containing an increased amount of newly formed fibrous or gliomatous tissue are present.

Chronic Meningo-encephalitis.[1]—This is a disease characterized by

[1] Alzheimer, "Histologische und Histopathologische Arbeiten über die Grosshirnrinde mit Besonderer Berücksichtigung der Pathologische Anatomie der Geisteskrankheiten." Herausgegeben von Frantz Nissl, vol. i. Halliburton, "Lancet," June 22, 1901. Soukhanoff and Gannouchkine, "Arch. de Neurol.," Sept., 1902, vol. 14. Folotchinoff, "Travaux de la Clinique des Maladies mentales et

chronic inflammation of the brain-substance and meninges, giving rise to gradual impairment of the mind and to general paralysis; the condition is known clinically as **dementia paralytica,** or **paresis.**

The disease seems to have some almost constant connection with syphilis, since in about seventy-five per cent. of all cases there is a history of an antecedent specific infection; traumatism, lead-poisoning, alcoholism, and prolonged mental strain have also been thought to be predisposing causes. The anatomic changes and clinical phenomena strongly support the view that the affection is due to a toxemia, the exact nature of which remains obscure.

Morbid Anatomy.—The lesions observed in this affection vary considerably, but those most commonly noticed are cortical atrophy, especially of the frontal lobes of the cerebrum, thickening of the dura, with the formation in some cases of a membrane on its inner surface, and condensation and opacity of the pia, which is thickened and abnormally adherent to the brain-substance.

Microscopically, small collections of lymphoid and plasma cells surround and form mantles over the blood-vessels, the walls of which constantly show more or less thickening, particularly of the adventitiæ. Destruction of many nerve-cells of the cortex occurs, and, as a consequence, degeneration of the axones that pass from them; these degenerations may be traced downward through the brain and cord. The tangential nerve-fibers lying in the molecular layer are, in severe cases, almost entirely destroyed. The protoplasmic processes of these cells are similarly affected. Along with these changes there is considerable formation of fibrous tissue in and around the vascular processes passing into the brain from the pia. The neuroglia cells are greatly increased in number, and the neuroglia fibers are sometimes thickened. The membranes show the usual microscopic evidences of chronic inflammation. All these morbid changes in the blood-vessels, neuroglia, and fibers lead to atrophy of the brain; the convolutions become flattened and shrunken; the weight of the organ is much less than normal. The most marked alterations are in the motor area and in the frontal lobes. The nerve-cells of the cord are often the seat of marked degenerative changes. The meninges of the cord are also much thickened; these changes are especially marked in the posterior portion of the cervical and dorsal cord, giving rise to pressure on the sensory nerve-roots, and thereby often causing considerable pain. Degeneration of tracts, especially of the posterior and lateral columns, has been observed in a large number of cases. The proteid content of the cerebrospinal fluid is usually increased, and the studies of Siemerling and others have shown that there is an almost constant lymphocytosis of this liquid, and that during periods of notable clinical activity the lymphocytes are most abundant.

Syphilis of the central nervous system,[1] exclusive of the parasyphilitic

nerveuses a Saint-Petersbourg," 1902, fasc. 1, pp. 1–210. Lawrence, "Jour. of Nerv. and Mental Dis.," Dec., 1903, p. 754. Diefendorf, "Amer. Jour. of Med. Sci.," Dec., 1903, p. 1047. Klippel, "La Sem. Méd.," Aug. 5, 1903, p. 255. None, "Fortschr. d. Med.," 1904, No. 28. Siemerling, "Berl. klin. Woch.," 1904, No. 21. De Buck, "Bulle. de la Soc. de Méd. Mont. de Belgique," Sept., 1904. Robertson, "Brit. Med. Jour.," Oct. 24, 1903, p. 1065. Cazeneuve, Thèse de Bordeau, 1904. Curion, "Nouv. iconographie de la Salpêtrière," 1905, No. 5. Marchand, "La Presse Méd.," April 8, 1905, p. 217.

[1] Migazzini, "Monatsch. f. Psychiatry u. Neurol.," March, 1902. Ingelrans,

affections (p. 180), occurs in about two per cent. of all cases of acquired syphilis. In the congenital form of the disease malformations of the brain, internal hydrocephalus, and imperfect development of the cortex are not infrequently present; such patients are also liable to the manifestations of acquired syphilis. The lesions of lues may be restricted to the brain, or to the cord, but in most cases both organs are involved. The toxin produced by the infecting organism exerts a deleterious influence on both motor and sensory neurones throughout the cerebrospinal axis, and as these alterations are rarely exactly the same in any two cases, it is apparent that the morbid anatomy and clinical manifestations of the disease often fail to conform to a definite series of phenomena. Aside from the specific toxic effect of the poison on the functionating elements of the brain and cord, the changes in the blood-vessels and meninges indirectly influence the nutrition of the brain and cord. The alterations of meningoencephalitis have already been considered (p. 870). Obliterative endarteritis affecting particularly the branches in the Sylvian area is frequently observed. In this manifestation proliferative changes occur in the subintimal layer of the affected vessels, followed by alterations in the endothelium, hyaline or fibro-hyaline transformation of the new tissue, reduction in vessel lumen and therefore diminished blood-carrying capacity and starvation of the tissues supplied by the affected arteries. Periarteritis and atheroma also occur. Thrombosis and softening are sometimes observed. The most frequent form of syphilis of the cord is a meningomyelitis characterized by some softening, congestion, and edema, often focal, or limited to small areas, especially in the lumbo-thoracic region. Histologically the affected areas are the seat of lymphocytic accumulation, degeneration of the myelin, and swelling of the axis-cylinders; proliferation of the glia occurs early in the process, but is generally conceded to be secondary to cell infiltration, and degenerative and necrotic changes. The pia and arachnoid are frequently thickened, infiltrated with lymphoid and plasma cells, and in some cases there is a notable exudate. Obliterative changes in the vessels are similar to those already described as occurring in the brain. When the condition has persisted for a considerable time, the areas of primary infiltration are, by proliferation of the neuroglia, converted into sclerotic areas, from which secondary degenerations commonly arise.

Gumma of the brain varies in size from a microscopic collection of lymphoid cells and fibrohyaline tissue to masses 5 cm. to 10 cm. in diameter. In gross gummata the consistency is rarely uniform, the periphery being soft, succulent, and vascular, and the center dry, firm, relatively bloodless, pale, and hyaline or containing yellowish caseous areas. Histologically the gumma (p. 179) is composed of masses of lymphoid and plasma cells, spindle-shaped and stellate connective-tissue elements, and a fibrohyaline matrix. The younger cell masses are at the periphery and the fibrous or fibrohyaline and caseous material near the center. Giant cells are occasionally present, but are inconspicuous. It is probable that gummata may be infected by tubercle

"Echo Méd. du Nord," April 3 and 10, 1904. Hirschl, "Wien. klin. Woch.," April 28, 1904 p. 465. Ogilvie, "Brit. Med. Jour.," July 16, 1904, p. 140. Mott, "Practitioner," July, 1904, p. 55. Barrett, "Amer. Jour. of Med. Sci.," March 1905, p. 390. Mooers, "Amer. Jour. of Insanity," 1904, No. 1.

bacilli, and that therefore mixed lesions occur. The larger masses press upon and destroy tracts, interfere with the vascular supply to contiguous tissues, and may, in this way, be associated with softening.

Tuberculosis of the Central Nervous System.[1]—Coincident with the eruption of miliary tubercles in the meninges, lesions of the same character may be produced in the brain-substance; the cortical portions are most frequently affected, though in some instances the deeper parts are also diseased. These miliary tubercles are gray or yellowish-white, and are softened in the center; hemorrhages sometimes occur around them. They are, of course, surrounded by an area of inflammatory tissue. These softened areas may coalesce, and much larger tubercles result. However, the large solitary tubercles generally occur as a result of the fact that but few tubercles were present, and the disease consequently ran a very protracted course, and each lesion had sufficient time to become large. The large tuberculomas (p. 153), also called conglomerate tubercles,[2] resemble the smaller ones, but may become infected by pyogenic organisms, and as a consequence their contents sometimes become puriform; they are most common in the cerebellum. Microscopically, the tubercles of the central nervous system in every way conform to similar bodies occurring elsewhere. Tuberculous meningitis may occur independently of lesions in the brain or cord, and is sometimes due to direct extension from contiguous osseous structures, especially in the bodies of the vertebræ. In a general way, tuberculosis of the meninges follows the usual types of tuberculosis of the serous membranes (p. 475). In some cases miliary infiltration of the pia-arachnoid occurs; in other instances the inflammation produces a sero-fibrinous exudation; there may be conspicuous accumulation of fluid in the interstices of the pia and arachnoid and accumulation in the ventricles. A definite tuberculoma, or circumscribed area of chronic caseous tuberculosis, is occasionally seen.

Multiple Sclerosis[3] **(Insular Sclerosis).**—In this disease there occurs throughout the entire central nervous system areas in which the neuroglia is greatly increased in amount and the individual fibers are thickened and probably elongated. As the neuroglia corresponds to the fibrous tissue of other parts of the body, its hyperplastic condition in these instances may be looked upon as analogous to the fibrosis occurring in the kidney, liver, and other organs. These sclerotic changes may also be compared to those tumors of the central nervous system called *gliomata*, as in both instances the tissue of which the new formation consists is hyperplastic neuroglia; indeed, it can not be said that there is any sharp line of distinction between the two conditions—the two bearing exactly the same relation to each other that newly formed fibrous tissue in organs bears to the fibromata. The process, which is a

[1] Trevelyan, "Lancet," Nov. 7, 1903, p. 1276.
[2] Barbacci, "Centralbl. f. allg. Path. u. path. Anat.," 1902, p. 833.
[3] Shoyer, "Jour. of Path. and Bact.," March, 1902. Bielschowsky, "Neurolog. Centralbl.," Aug. 16, 1903. Straühuber, "Ziegler's Beitr.," 1903, Bd. 33, p. 409, also "Neurolog. Centralbl.," Jan., 1904, Bd. 23, No. 2. Spiller, "Amer. Jour. of Med. Sci.," Jan., 1903. Bramwell, "Review of Neurol. and Psych.," Jan., 1903 Borst, "Lubarsch and Ostertag's Ergebnisse der allg. Path. u. path. Anat.," Neunter Jahrg. Abt. I, 1903, p. 67. Tredgold, "Review of Neurol. and Psych.," July, 1904. Müller, "Die Multiple Sklerose d. Gehirns u. Ruckenmarks," Jena, 1904. Dercum and Gordon, "Amer. Jour. of Med. Sci.," Feb. 1905, p. 253.

very chronic one, sometimes follows such diseases as influenza, malarial and typhoid fevers, but there is no conclusive evidence that they are the cause; the same is true of syphilis and trauma. The sclerotic areas vary much in size, some being only microscopic and others involving an entire lobe of the brain; the nodules may be scanty or numerous, often the latter, and are irregularly distributed in both brain and spinal cord; they show no tendency to follow tracts. In the white substance the areas of sclerosis, when sufficiently large, may be detected by their pinkish color, and by being considerably harder than the neighboring normal brain tissue; in the gray substance they are so nearly the same color as the normal tissue that it is very difficult to distinguish them. In some cases the neuroglia just beneath the epithelial lining of the ventricles becomes hyperplastic, and the resulting condition is called **ependymal sclerosis.** The sclerosis may be diffuse, giving rise to a condition of uniform thickening, or it may occur in many minute circumscribed areas; the former variety of the disease is called **smooth,** and the latter **granular ependymal sclerosis.** There is a form of sclerotic change known as **lobar sclerosis,** affecting one or more lobes of the brain, and sometimes the entire brain. The condition seems to have, in the beginning, some relation to the cerebral blood-supply, as the lesion nearly always corresponds to the distribution of some artery. The entire region involved is very hard, the gyri are depressed, and the pia is adherent. Secondary degenerations are more pronounced in this form than in the other varieties.

FIG. 411.—DISSEMINATED SCLEROSIS.—(*Gordon.*)
Areas of sclerosis in the pyramids and nuclei of the medulla. The sclerotic areas are unstained.

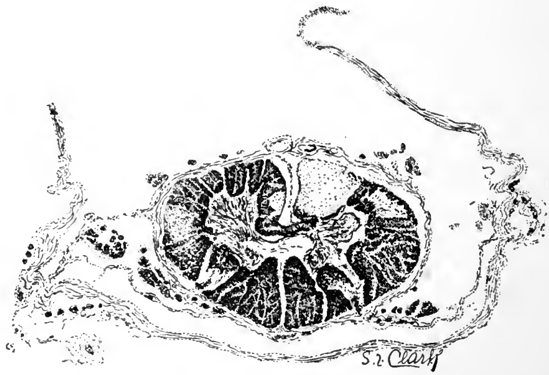


FIG. 412.—DISSEMINATED SCLEROSIS.—(*Gordon*).
Areas of sclerosis in pyramidal tracts, Gowers' tract, and direct cerebellar tract. Weigert's method; the sclerotic areas are unstained.

Microscopically, the sclerosed area is composed of hypertrophic or hyperplastic neuroglia fibers (demonstrable by the method of Mallory, see p. 840), and the neuroglia cells are also greatly increased. The nervous elements show more or less evidence of degenerative changes;

the myelin sheaths of the nerves are largely destroyed, but, strange to say, the axis-cylinders do not exhibit, as a rule, marked alterations; they are, in the majority of cases, preserved, and this integrity explains the absence of secondary degenerations in the various tracts. It is to be remembered, therefore, that the characteristic histologic feature of multiple sclerosis consists of proliferation of neuroglia and destruction of myelin sheaths of nerve-fibers, without system degeneration of any tract. The morbid changes are more pronounced around the small blood-vessels, the walls of which are usually thickened and frequently show more or less hyaline transformation. Compound granule cells (p. 865) are often found in the sclerosed areas. Other bodies, the result of degenerative change, are also frequently encountered in these lesions—namely, the *corpora amylacea.* They are rounded or oval structures, generally somewhat larger than nerve-cells, containing no nuclei, and staining brown with iodin, and a dark-blue color with toluidin-blue.

Tumors of the brain[1] may be primary or secondary. Probably the most frequent primary cerebral tumor is a new growth, peculiar to the central nervous system, called *glioma.* The tumor is usually found in the cortical portion of the cerebrum, and, as a rule, does not protrude notably beyond the surface. On section it is found to consist of a gray or grayish-red substance, which often contains whitish spots and hemorrhagic foci; some parts of the tumor are not uncommonly of a gelatinous consistency. Blood may be extravasated into the tumor to such an extent that it has the appearance of a massive hemorrhage into the cerebral tissue. It sometimes happens that the brain-substance in the vicinity of the tumor is more or less softened as a result of the pressure exerted by the neoplasm.

Microscopically, these tumors consist of hyperplastic neuroglia; there is an enormous increase in the number of the glia cells, and the neuroglia fibers around them are thicker than normal and are far more numerous than in the normal brain. In the center of the tumor neither nerve-cells nor axis-cylinders are found, but if the growth gradually merges into the contiguous nervous substance, as it not infrequently does, the edges of the tumor contain these elements, and the margin of the neoplasm is proportionately diffuse and ill-defined. The blood-vessels are usually very large and numerous; their walls often show hyaline degeneration, and the outer coats are sometimes thickened.

If the tumor contains nerve-cells, with or without nerve-fibers, it is called *ganglionic neuroglioma.* If such neoplasms involve the white matter of the convolutions or the centrum ovale, nerve-cells are fre-

[1] Hartmann, "Wien. klin. Woch.," May 22, 1902. Gilbert-Ballet and Armand Delille, "Nouv. Iconograph. de la Salpêtrière," May and June, 1902, pp. 201–222. Philippe, Cestan and Oberthur, "Revue Neurolog.," Aug. 31, 1902, p. 810. Bielschowsky, "Deut. Zeit. f. Nervenheilk.," 1902, Bd. xxii. Saxer, "Zieg. Beitr.," 1902, Bd. xxxii. Siefert, "Münch. med. Woch.," May 20, 1902. Hollis, "Lancet," March 28, 1903, p. 884. Starr, "Jour. Nerv. and Ment. Disease," July, 1903. p. 398. Blackburn, monograph entitled "A Study of 29 Cases of Intracranial Tumor found in 1642 Postmortems in Cases of Mental Disease," Washington, D. C., 1903. Woolsey, "Amer. Jour. of Med. Sci.," Dec., 1903, p. 956. Kufs, "Arch. f. Psych. u. Nervenkrank.," 1904, Bd. xxxviii, No. 3. Stoerk, "Wien. klin. Woch.," 1904, No. 7, p. 184. Iumucopulo, "Arbeit. a. d. Neuro. Inst. a. d. Wiener Univ.," 1904, Bd. xi. Walker, "Jour. of Path. and Bact.," Nov., 1904, p. 81. Weisenburg, "N. Y. Med. Jour.," Feb. 11, 1905, p. 281; also, "Proceed. of Path. Soc. of Phila.," Feb. 28, 1905, p. 102.

quently present. These tumors resemble the simple glioma, and, with the exception that they contain, in addition to the neuroglia, the other elements of normal nervous substance in small quantity, they are identical. (See Glioma, p. 320.) Gliomatous tumors appear to owe their origin to defects in development. The new growth may, to a certain extent, present the appearance of *sarcoma*; under these circumstances the tumor is a mixed one, and may be called a *gliosarcoma*; at present the term gliosarcoma is in disrepute, and I believe deservedly so; it is extremely doubtful if the two neoplasms are in any way related, or are ever concurrent.

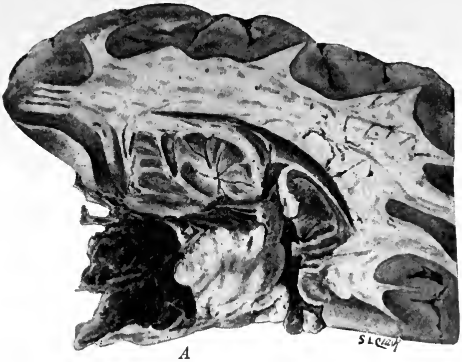


FIG. 413.—SARCOMA OF BRAIN.
Mesial part of inferior frontal convolution. (Dr. Funke's case.) *A*. Tumor, in the left half of which considerable hemorrhage has occurred.

Sarcomata of the brain occur with less frequency than the gliomata. The tumors show the usual tendency to remain, in a measure, distinct from the normal structure of the part, though to a varying degree they infiltrate contiguous tissues, especially the membranes. The meninges in the vicinity are often in-

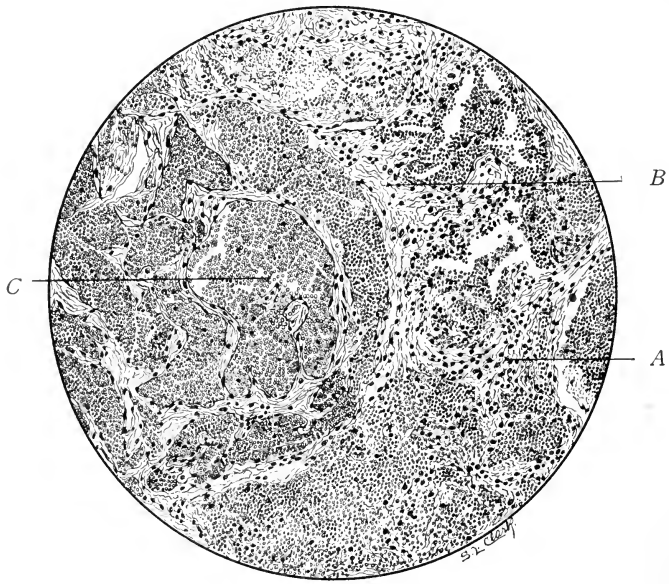


FIG. 414.—SARCOMA OF BRAIN.
Mesial part of inferior frontal convolution. (Dr. Funke's case.) *A*. Cellular areas; mostly spindle cells. *B*. Areas of hyaline fibrous tissue. *C*. Large blood-channel. There are many smaller channels, some of which have ruptured, causing interstitial hemorrhage.

flamed, and the adjacent nerve substance is usually more or less softened. Within the tumors, hemorrhages and softening often occur. In certain forms of cerebral sarcoma, parts of the neoplasm become calcified, and the tumor is called a *psammoma* (p. 359).

Angiomata of the brain sometimes occur; the tumors are quite small, but may be multiple. They appear as small red extremely vascular areas and are probably of congenital origin. *Fibromata* are very rare cerebral tumors. *Osteomata, lipomata*, and *cholesteomata* are occasionally seen. *Carcinomata* are usually secondary; such masses possess the architecture and peculiarities of the variety of tumors from which they originated. A not infrequent manifestation of cancer results from extension into the spinal canal of secondary growths arising in the bodies of the vertebræ; this condition is commonly a sequence of carcinoma of the mammary gland. *Primary carcinoma* may, however, occur, beginning in the epithelial cells of the ventricles. Secondary sarcomata are also sometimes observed. Tumors arising from pigmented moles (p. 357) frequently manifest metastasis to the brain; the growths are usually multiple (see Fig. 205, p. 358). Both primary and secondary malignant tumors of the brain are commonly infiltrated by blood and may be mistaken for areas of hemorrhage. This statement applies to most neoplasms, but is particularly true of chorioepithelioma (p. 354).

Cysts of the Brain.[1]—*Dermoid cysts*, which are sometimes multiple, are occasionally observed in the cranial cavity. *Cystic dilatation of the fourth ventricle*, due to the occlusion of the orifice by which its fluids are drained, sometimes occurs. Parasitic cysts (*cysticercus* and *hydatid*) may be situated in the brain tissue, or choroid plexus, or be free in the ventricular cavities.

Tumors, cysts, gummata, tuberculomata, and actinomycotic masses give rise to important structural alterations in the contiguous brain tissue, and, if occupying certain locations, press upon tracts and induce secondary degenerations (p. 860). Irritation produced by the mass may cause inflammation of the adjacent brain tissue or meninges. Interference with the circulation sometimes causes softening; pressure on the aqueduct of Sylvius prevents escape of fluid from the ventricles and gives rise to internal hydrocephalus.

Diseases of the Pituitary Body.[2]—Enlargement, or tumor formation affecting this body has frequently been observed in acromegaly (see p. 806); twenty-five tumors of the hypophysis without acromegaly are on record, and numerous cases of the latter affection, in which no structural lesion could be demonstrated in the pituitary, have been reported. **Tuberculosis** and **gummata** are occasionally found in the

[1] Diamond, "Jour. Amer. Med. Assoc.," June 17, 1899. Askanazy, "Deut. med. Woch.," June 12, 1902. Reggiardo, "Semana Medica," Buenos Ayres, 1903, No. 47. Salvador and de Leon, Thèse de Paris, 1903, No. 358. Maragliano, "Gaz. degli Osped. e. delle Clin.," March, 1904, vol. xxv. Alquier and Courtellemont, "Revue Neurol.," June 30, 1904, p. 635. Hunt, "Amer. Jour. of Med. Sci.," March, 1904, 494.

[2] Erdheim, "Zieg. Beitr.," 1903, Bd. 33, p. 158. Berger, "Zeitsch. f. klin. Med.," Bd. liv, 5, 6. Guerrini, "Centralbl. f. allg. Path. u. path. Anat.," March 15, 1905, p. 177. Zak, "Wien. klin. Rundschau," Bd. xviii, Nos. 9 to 11. Kollarits, "Deut. Zeit. f. Nervenheilk.," Bd. xxviii, No. 1. Stadelmann, "Zeit. f. klin. Med.," Bd. 55.

pituitary body. The organ is rarely the seat of tumors. The most common of these are *adenomata,* which are composed of hyperplastic follicles of the anterior lobe of the body. *Carcinomata, sarcomata, endotheliomata, lipomata,* and *teratomata* have been observed.

Diseases of the Pineal Gland.—This body is very rarely the seat of primary disease. The most frequent alteration is an increase in the quantity of the *calcareous material* contained within it, and *cystic degeneration* is sometimes encountered. Tumors are very rare.

Diseases of the Larger Blood-vessels of the Cranium.—The great vessels at the base of the brain not infrequently become diseased. The most frequent change observed is *atheroma.* (See p. 520.) *Aneurysms* are not common, but are occasionally encountered.

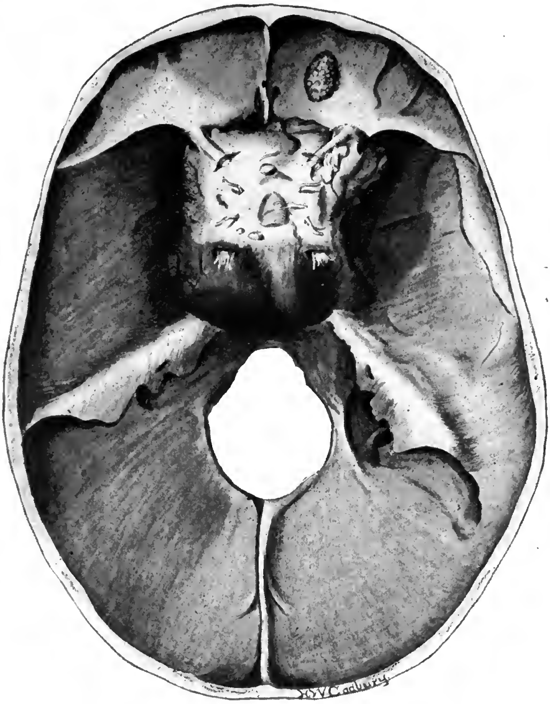


FIG. 415.—ENDOTHELIOMA OF PITUITARY BODY.
The growth has extended into the right orbit and penetrated the orbital plate of the frontal bone from below upward. (Dr. Burr's case.)

THE SPINAL CORD.

Remarks on the Functions of the Gray and the White Matter of the Cord.—A comprehension of the diseases affecting the spinal cord is facilitated by a knowledge of the function of the different parts, and for this reason the following brief summary is given: Anatomically the spinal cord consists of a central mass of gray matter, on transverse section shaped something like the letter H, surrounded by white substance. The latter structure is uniformly composed of fibers and is therefore homogeneous; a knowledge of the physiology of this part of the cord shows that the white substance consists of tracts or systems of fibers possessing different functions. The posterior columns (*tracts of Goll and Burdach*) are sensory in function and are physiologically connected with the posterior root and spinal ganglia, from which the major part of the fibers arise. Sensory stimuli coming from the peripheral nerves are transmitted through the spinal ganglia and posterior root to the columns forming the posterior tracts of the cord. It will therefore be seen that a lesion of the sensory pathway, between the spinal ganglia and the cord, or within the latter structure, severs the fibers from their ganglion cells and gives rise to a degeneration of the posterior columns

(ascending degeneration). The posterior columns conduct chiefly the stimuli necessary to the sense of touch and the sense of coordination in station and gait, and therefore a lesion of these structures interferes with the transmission of sensory impulses and disturbs the necessary connection between certain forms of sensation and coordinated motion.

The *direct and crossed pyramidal tracts* are exclusively motor in function. As the fibers contained within these areas originate in the motor area of the brain, a lesion affecting the latter or severing the fibers emanating from it necessarily induces a descending degeneration of the two tracts in the cord. Functionally the *anterolateral column* (Gowers' tract) conducts pain and temperature sensations. The *posterolateral* or *direct cerebellar tract* is directly connected with the cerebellum and, functionally, controls the equilibrium of the body. The last two tracts originate in the cells of Clarke's columns, transmit impulses upward, and consequently degeneration affecting their fibers is of the ascending type.

Gray Matter of the Cord.—The *anterior cornua* consist chiefly of multipolar cells (p. 835) the axis-cylinders of which form at their exit from the cord the anterior roots; the latter are continuous with the motor fibers of the nerve-trunks to the periphery of the body. Consequently a destructive lesion of the anterior cornua will be followed by motor symptoms — paralysis. On the other hand, it is well known that when the anterior cornua are diseased, trophic disturbances, especially in the muscles, constantly follow. Therefore the anterior cornua have a double function—motor and trophic. As to the posterior cornua, an isolated lesion of their cells is rare. The function of the cells of Clarke's columns is mentioned above.

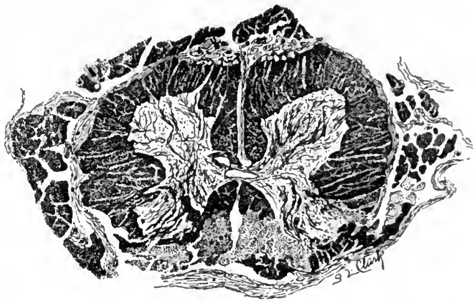


FIG. 416.—SECONDARY DEGENERATION OF POSTERIOR COLUMNS DUE TO PRIMARY LESION IN THE POSTERIOR ROOTS. —(*Gordon.*)

The degenerated parts (sclerotic areas) are unstained.

Circulatory Disturbances.—*Active hyperemia of the cord* probably occurs only in the beginning of inflammation; it is certain that we know nothing of hyperemia from other causes. Passive hyperemia may result from the recumbent posture if the individual be very weak. The cord would probably appear, under those circumstances, of a darker color than normal.

Anemia of the cord occurs under the same circumstances that give rise to a like condition of the brain; exhausting hemorrhages, chlorosis, pernicious anemia, leukemia, and all of those diseases accompanied by lessened richness of the blood may cause the condition. The affected cord is paler than normal on removal, but the warning given in connection with hyperemia and anemia of the brain (see p. 857) applies with equal force here. The changes in the spinal cord accompanying pernicious anemia[1] consist of a diffuse degeneration affecting all the tracts

[1] Billings, "Chicago Med. Recorder," Jan., 1903, p. 1. Taylor, "Brain," Spring, 1904, p. 27.

and a more marked degenerative change the conspicuous lesions of which are situated in the posterior and lateral columns; the alteration resembles combined sclerosis, but lacks uniformity in distribution. The gray matter as well as the spinal ganglia are notably not affected.

Hemorrhages into the cord are usually the result of rupture of a blood-vessel from injury; this is especially the case if the hemorrhage be at all large. Minute hemorrhages sometimes occur into the substance of the spinal cord during acute disease; the blood may be extravasated into the central canal of the cord. The condition is called **hemato-myelia.**[1] The extravasated blood causes dissociation and disintegration of the nerve-fibers and cells of the affected area; an inflammatory reaction occurs in the contiguous tissues, which are infiltrated with mononuclear leukocytes and contain numerous granule cells. If the

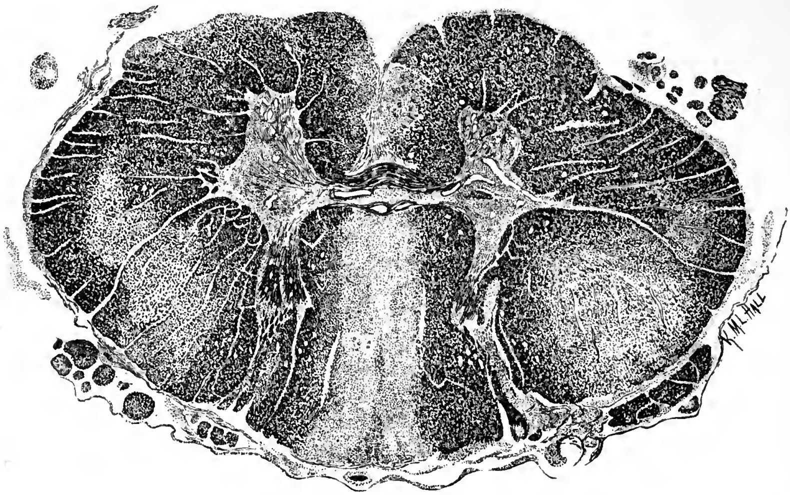


FIG. 417.—SPINAL CORD.
Areas of sclerosis due to pernicious anemia. The sclerotic parts are unstained. Weigert's method.

patient survive, the blood may be absorbed; a cyst sometimes forms, and the glia at the margin of the lesion proliferates. As a result of the destruction of fibers secondary degenerative changes develop.

Myelitis or inflammation of the cord[2] may be *acute*, *subacute*, or *chronic*, depending on the cause. The acute and subacute forms occasionally become chronic. There are several varieties of myelitis that show sufficiently distinctive features to merit separate description, but the form meant when the term myelitis is used without qualification will be first considered.

[1] Bruce, "Scottish Med. and Surg, Jour.," Aug., 1902, p. 107. Laignel-Lavastine, "Nouv. Iconograph. de la Salpêtrière," May and June, 1904. Collins and Zabriskie, "Med. Record," Sept. 3, 1904, p. 361.

[2] Erb, "Brit. Med. Jour.," Oct. 11, 1902, p. 1114. Singer, "Brain," 1902, Part II, 332. Stewart, "Trans. Path. Soc. of London," 1902, vol. 53, p. 1. Weill and Gallavardin, "Revue Neurolog.," Oct., 1903, p. 999. Collier, "Brain," Spring, 1904. Ghilarducci, "Il Policlinico," Rome, 1904, No. 25. Collins, "Jour. of Nerv. and Ment. Dis.," Nov., 1904, p. 695. Baudron, "Annals Medico-Chirurg. du Centro," Nov. 21, 1904. Rhein, "Univ. of Penna. Med. Bull.," Jan. 1905, p. 373.

Perhaps the most frequent cause of myelitis is injury to the cord. Closely related to this are those inflammations, always more or less chronic, that are the result of the long-continued pressure of tumors, aneurysms, and cysts, and of the compression exerted by deformed vertebræ in caries of these bones.

Myelitis, secondary to inflammations of the pia-arachnoid, often occurs; it is, therefore, present in cerebrospinal meningitis, tuberculous meningitis, and other infective lesions of these membranes. In such conditions as pyemia, septicemia, and other diseases in which bacteria are present in the blood myelitis is occasionally observed; it is usually of a suppurative character, and is accompanied by a similar process in the cerebral tissues. To this class probably belong those inflammations of the cord that follow smallpox, rheumatism, typhoid fever, and typhus fever. Sexual excesses, the suppression of the menses, and cold are supposed sometimes to occasion the disease; at most they are nothing more than predisposing factors. Acute myelitis is probably always infective, toxemic, traumatic, or embolic. Syphilis is a frequent cause of the chronic form.

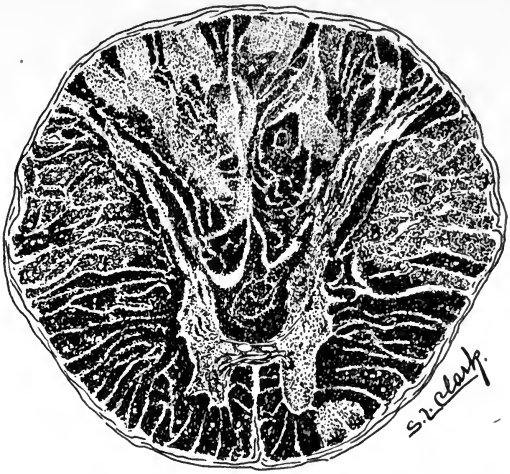


FIG. 418.—MYELITIS. AREAS OF SOFTENING IN THE CORD DUE TO TUBERCULOSIS OF THE VERTEBRÆ.

Morbid Anatomy.—Both the white and gray matter may be affected. If the white substance be alone attacked, the disease is called **leukomyelitis**; if the inflammation be confined to the gray matter, the condition is termed **poliomyelitis.** The entire thickness of the cord may be diseased, in which case the affection is called **transverse myelitis.** If an extensive area be involved, the myelitis is said to be *diffuse;* if a small area alone of the cord be the seat of the disease, the condition is termed *focal myelitis;* when many foci of inflammation are present, the condition is known as *disseminated myelitis.* Inflammation just around the central canal and extending more or less into the surrounding gray substance is called *central myelitis;* the anterior cornua may be also affected without disease in other parts of the gray matter—*anterior poliomyelitis.*

On examination, the meninges in the vicinity of the diseased area are found to exhibit more or less evidence of inflammation. The cord is usually swollen and softened, and on section presents a reddish appearance. If the inflammation be intense, the substance of the cord is almost creamy in consistence; and if the amount of blood extravasated into it be considerable, the diseased area is said to be in a state of *red softening.* At a later period the pigment contained in

the effused blood undergoes changes, converting the softened tissues into a yellow, and finally a white substance, and the last two conditions are therefore called *yellow* and *white softening* respectively. If the disease be subacute or chronic, the cord may be either of a normal, increased, or diminished consistence; it usually presents a grayish appearance, as a result of proliferation of the neuroglia; late in the disease small cavities in the affected area are occasionally encountered.

Microscopically, the blood-vessels are found to be greatly dilated in the acute forms, and there is often considerable blood extravasated into the affected tissues. The myelin sheaths of the nerves swell and become nodose, exhibiting here and there small areas of fatty degeneration; the axis-cylinders are swollen and granular, and finally disintegrate. The nerve-cells at first manifest tigrolysis, chromatolysis, and plasmolysis, in the order named, and later are necrotic or fatty; they are vacuolated, the chromophilic substance no longer stains, and, finally, disintegration occurs. The glia cells in acute cases undergo but little change, though they are usually somewhat swollen and increased in number. As the process grows older, and if it be pronounced, there remains of the original nerve elements scarcely more than a few fragments; compound granule cells (phagocytes) may appear in considerable numbers. If the diseased tissues contain blood, many cells, called pigment granule cells, may be seen containing the pigments of the disintegrating blood. At a later period the granular detritus resulting from destruction of the nervous elements disappears, connective-tissue cells make their appearance, more or less fibrosis occurs, and the neuroglia fibers greatly increase. Corpora amylacea often form in the tissues as the process becomes old.

Secondary degenerations (p. 860) of the columns of the cord commonly follow myelitis; the nature and extent of these depend on the situation and size of the primary lesion in the cord. From the initial focus, whatever its character, the degeneration proceeds along the nerve-fibers in the same direction in which impulses were carried before the injury occurred; this depends upon the fact that the axis-cylinders, being essentially a part of the nerve-cells from which they take their origin, are no longer properly nourished after separation from the body of the cells. Lesions of the cord, therefore, cause descending degeneration in motor fibers and ascending degeneration in the sensory columns. As myelitis may affect any of these structures it is possible to have alterations resembling those observed in the true system diseases; thus, if the posterior columns are involved, the alterations resemble tabes. If the lateral columns are affected, the form is that of primary lateral sclerosis, and when both lateral and posterior tracts are attacked, the lesion assumes the characters of a combined sclerosis. These varieties are observed only in the chronic cases of myelitis after the secondary degenerations are definitely established.

Acute ascending paralysis[1] (Landry) is a name applied to a clinical syndrome the anatomic basis of which is probably not always the same.

[1] Sherman and Spiller, "Phila. Med. Jour.," March 31, 1900. Diller, "Jour. of Nerv. and Ment. Dis.," Oct., 1902, p. 577. Rolly, "Münch. med. Woch.," July 28, 1903, p. 1283. Preobragenky, "Arch. de Neurol.," 1904, xviii, p. 87. Gordinier, "Albany Med. Annals," Jan., 1904. Hey, "Münch. med. Woch.," Dec. 20, 1904.

In many cases the clinical history and anatomic findings indicate that it is a form of neuritis and should be considered with inflammations of nerves. In such instances no conspicuous alterations are found in the spinal cord. In other cases inflammatory lesions have been observed in the anterior cornua justifying the name **acute ascending poliomyelitis.** In some of the reported cases the motor nuclei of the brain were also affected (*acute polioencephalomyelitis*). I shall refer only to the changes that are present in the cord in cases in which the anterior horns have been found affected. All observers are agreed that it is the result of intense toxemia or is due to infection. Gordinier states that the following organisms have been isolated from the lesion: Streptococci, staphylococci, typhoid bacilli, the anthrax bacillus, and a number of unidentified bacteria. It may, therefore, be assumed that the disease is often, if not always, a manifestation of infection.

Morbid Anatomy.—The cord frequently shows no gross evidence of disease; in other cases some redness of the gray matter and occasional hemorrhagic areas in its substance have been observed. Microscopically, the gray matter of the cord, medulla, pons, cerebrum, and cerebellum exhibit the usual changes of beginning inflammation: The vessels are distended with blood, and around many of the smaller veins and the capillaries collections of lymphoid cells are usually present; the nerve-cells manifest the alterations usual in inflammation; the white matter is sometimes slightly, but evidently only secondarily, affected. Inflammatory changes have been observed in the nerve-roots and peripheral nerves.

Acute poliomyelitis[1] has been attributed to the same general causes believed to induce the ordinary forms of inflammation of the cord, but there are many facts indicating that it is a distinct disease—the result of a specific cause having a predilection for this particular part of the nervous system. Several experimenters have successfully inoculated monkeys in which the disease runs a typical course, and may be transferred in series. The virus is contained in the cord, brain and mucosa of the nasopharynx, passes through a Berkefeld filter, may be preserved by glycerination, and in other respects resembles the virus of rabies. Its exact nature is unknown. The disease, under natural conditions, is feebly communicable; children at about the time of first dentition are most susceptible although adults are not immune. Numerous epidemics have been observed; in some of these adults have occasionally suffered and even domestic animals have been attacked. Experimental and clinical studies indicate that the incubation period is between four and thirty-three days, the average being about ten days.

Morbid Anatomy.—In acute cases the membranes are usually hyperemic, especially in the lumbar and cervical enlargements. In autopsies made shortly after death the cord presents no conspicuous alteration in density; later, autolytic changes produce softening. The vessels, especially in the grey matter, are intensely distended and minute hemorrhages are present. If death occur during the attack the microscope shows that both meninges and cord are affected. The former usually present a round cell perivascular infiltration. Although the white matter is involved the most striking lesions are in the grey matter, especially in those areas corresponding to the origin of nerves

[1] Flexner and Lewis, "Jour. of Exp. Med.," March 14, 1910, p. 227. Strauss and Huntoon, "N.Y. Med. Jour.," Jan. 8, 1910, p. 64.

supplying the paralyzed muscles. Lymphoid infiltration occurs in the anterior and posterior horns and in the commissure. The nerve cells at first show swelling, loss of chromophilic substance, granular protoplasm and imperfectly stained nuclei; later these cells undergo necrosis, and are surrounded or infiltrated by leukocytes, most of which are mononuclear and of the lymphoid type, although the polynuclear variety may participate. Areas of rhexis are often conspicuous. In animals, and in some cases in man, similar changes are present in the medulla and brain. The intervertebral ganglia show diffuse and nodular infiltration by lymphocytes which are particularly abundant about the nerve cells and fibers, both of which may be degenerated and necrotic. The most conspicuous clinical phenomenon is the muscular paralysis and as the affection is largely restricted to childhood, it is called **infantile paralysis.** In cords examined long after the acute stage the affected areas are firmer than the contiguous cord; the glia cells and fibers are notably increased and the nerve cells normally present proportionately decreased or in areas absent. An interesting feature of this disease is that the motor cortex, in connection with the destroyed areas in the cord, appears in the course of time to undergo more or less atrophy. The peripheral nerves arising from the affected nerve cells naturally degenerate and the muscles supplied atrophy. As the permanent paralysis depends upon the location and extent of the nerve cell destruction, and as many cells, primarily involved, recover, the muscle disturbance is most marked at the height of the attack and muscles initially paralyzed may later be restored.

Chronic Anterior Poliomyelitis[1] (*Progressive Muscular Atrophy of Spinal Origin*).—Closely related to acute anterior poliomyelitis in the seat of its spinal lesions is the disease known as progressive spinal muscular atrophy. It is not, however, at all certain whether the changes in the gray matter of the cord are to be regarded as of an inflammatory or of a degenerative kind, and it would therefore be obviously incorrect at the present time to class them with the inflammations; notwithstanding the uncertainty that still exists respecting its character, the disease is called chronic anterior poliomyelitis. In this connection attention should be directed to the fact that injury, overwork, exposure to cold, or an attack of any of the infectious diseases are regarded as the most frequent causes of the affection; as these are precisely the etiologic factors generally looked upon as being most potent in the production of ordinary myelitis, and as the lesion of progressive muscular atrophy could be very well the result of an inflammatory condition, it certainly requires no very great stretch of the imagination to conceive a closer relation between the two than is generally supposed.

Morbid Anatomy.—The gross changes in the cord are never very intense; hyperemia is absent; in marked cases the anterior cornu may be manifestly smaller than normal. Histologically, the conspicuous changes involve the motor cells of the anterior cornua. Mott states that of the three groups of cells, occupying the anterior horn, the outer and middle disappear; those of the inner group are less involved. Normal and wasting cells sometimes lie side by side. The ganglion cells in

[1] Mott, "Practitioner," May, 1904, p. 639. Herbert, Morley, Fletcher and Batten, "Brain," 1903, Part IV, p. 473.

process of disappearing are the seat of tigrolysis, chromatolysis, and plasmolysis. Later pigmentation appears within the cell, and finally small granules occupy the spaces previously filled by the cells. As the ganglion cells waste the neuroglia proliferates. The condition is believed to be a primary decay of the neurones. The alterations in the muscles are those of a progressive atrophy (p. 788). The nerve-trunks to the affected areas contain about half the normal number of fibers, and these are sensory.

Amyotrophic lateral sclerosis[1] is characterized by destruction of the anterior cornua and sclerosis of the motor tracts; it is, therefore, a chronic anterior poliomyelitis with degeneration of the pyramidal columns. In advanced cases, of long duration, changes have been observed in the medulla, pons, crura, internal capsule, and even in the cells of the motor area in the cortex. The first manifestations of the disease are usually observed in the cervical cord, although it may begin in the medulla. In some cases the onset is in the anterior cornua, in others the pyramidal tract appears to be first involved; the disease is essentially progressive. It will be observed that in chronic anterior poliomyelitis the lower segment of the motor neurone alone is involved, while in amyotrophic lateral sclerosis, both upper and lower segments participate in the degenerative and sclerotic process.

Progressive Bulbar Paralysis (*Glossolabiolaryngeal Paralysis*).—Very closely related to progressive muscular atrophy is a disease of the medulla known as progressive bulbar paralysis. It attends conditions similar to those accompanying progressive spinal muscular atrophy, and even passes into it by gradual stages, or vice versâ. In fact, the only difference between the two seems to be the mere accident of location, one affecting principally the cervical region of the spine, and the other the medulla, which is but the cord continued into the skull. With the exception of the difference in location, the two affections have exactly the same gross and microscopic anatomy. The disease is characterized by a primary and systematic lesion of the nuclei of the cranial motor nerves located in the lower half of the medulla, namely, of the seventh, ninth, tenth, eleventh, and twelfth nerves. According to Charcot, the lesion of the nucleus of the hypoglossus is the most pronounced. The changes in the cells of the affected nuclei are identical with those occurring in the ganglion cells of the cord in anterior poliomyelitis. The roots of the nerves which emerge from the nuclei undergo atrophy and sclerosis. The muscles supplied by diseased nerves also undergo atrophic changes, which consist of fatty degeneration and disappearance of muscle substance, proliferation of the nuclei of the sarcolemma, and increase of adipose and fibrous connective tissues. These changes are found in the muscles of the lips, tongue, pharynx, and larynx.

Insular Scleroses of the Cord.—In discussing insular sclerosis of the brain (p. 873) mention was made of the fact that here and there small areas in the cord were also affected, and it will, therefore, not be necessary again to refer to a spinal form of the affection.

[1] Mott, "Practitioner," May, 1904, p. 639. Dercum and Spiller, "Trans. of the Amer. Neurolog. Assoc.," 1898. Spiller, "Univ. of Penna. Med. Bull.," Jan., 1905, p. 390. Collins, "Amer. Jour. of Med. Sci.," June, 1903.

Tabes,[1] also called *posterior spinal sclerosis* and *locomotor ataxia*, is the most common and typical of the system diseases affecting the cord. The process is clearly traceable to syphilis in from eighty per cent. to ninety per cent. of the patients; it is also possible that alcoholic excesses, exposure to cold, over-exertion, and injury are responsible for a small percentage of the cases. Exactly how the syphilitic poison induces the change has not been definitely determined. The theory that the lesion was primary in the ganglia of the posterior roots has not been supported by the results of extended inquiry. It has been supposed that the posterior roots are involved in a meningeal inflammation acting

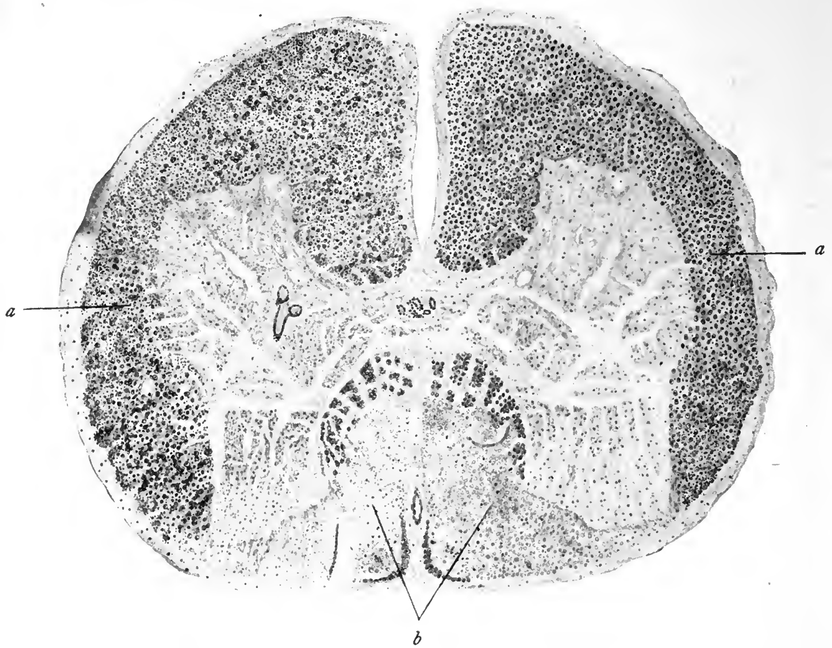


FIG. 419.—SPINAL CORD, SHOWING POSTERIOR SCLEROSIS.
Tissue was hardened in Müller's solution; sections stained in alkaline toluidin-blue. *a*, *a*. Normal nerve-fibers. *b*. Sclerotic area.

between the ganglia and the point where the fibers enter the cord, probably in the arachnoid.

Morbid Anatomy.—On removal the cord generally presents, in advanced cases, a striking diminution in its anteroposterior diameter, owing to the fact that the sclerosed tissue that has taken the place of the nerve-fibers occupies less space than the normal nerve substance. The

[1] Marie and Guillain, "Revue Neurolog.," Jan. 31, 1903, p. 49, also discussion p. 103. Mott, "Arch. of Neurology of London County Asylum," 1903. Collins, "Med. News," Jan. 3, 1903, and June 13 and 20, 1903; also "Jour of Nerv. and Ment. Dis.," June, 1903. Weigert, "Neurolog. Centralbl.," Aug. 16, 1904, p. 738. Erb, "Berl. klin. Woch.," 1904, Nos. 1 to 4. Hassin, "Med. Record," Jan. 30, 1904, p. 168. Möbius, "Jahr. der in. und ausland. Gesem. Med.," Jahrgang, 1904, Heft 1. Gowers, "Brit. Med. Jour.," Jan. 7, 1905.

newly formed tissue is also of a darker color than the neighboring normal parts, and on section its consistence is found to be increased. The disease, as a rule, first appears in the lumbar region, and is most intense in this situation; however, in severe cases the entire posterior columns of the cord may be involved. The posterior nerve-roots may also show marked sclerotic change.

Microscopic examination shows that the fibers of the posterior column have almost entirely disappeared, and in their place is a dense network of neuroglia tissue. In the early stages fatty particles may be seen occupying the places of the nerves. In the later stages corpora amylacea are numerous. In the upper portion of the cord the substance of the entire posterior columns is not affected, the disease here being limited to the posterior median tracts—column of Goll. Even in the lower parts of the cord some of the fibers always escape; a small band just beneath the pia, and on each side of the posterior part of the posterior median septum, is usually intact, as are also some fibers in the anterior part of the posterolateral column. If the disease be severe and of long standing, more or less sclerosis may be observed throughout the entire cord. For a more detailed description of the minute changes in the sclerosis of the nerve tissues occurring in this disease the reader is referred to the article on Insular Sclerosis of the Brain, page 873. The gray matter is not greatly affected in posterior spinal sclerosis, but degenerative changes occur in the ganglion cells of the posterior cornua and in the nerve-fibers of the gray matter, especially those surrounding the vesicular columns of Clarke. The nerve-cells in the spinal root ganglia as well as the posterior roots also degenerate; in some cases, usually advanced, the sensory nerves of the periphery show similar alterations.

From what has been said it will be seen that the disease does not affect the motor nerves, and, although incoordination in movement is a symptom of the malady, the muscles are not the seat of important alterations. Arthropathies (p. 830) also occur. The incoordination is entirely the result of a failure of the sensory nerve to convey the usual impulses to the sensorium, and a consequent vacillation on the part of the nerve-center, from a lack of knowledge as to the relation of the body to surrounding objects. See remarks on physiology of the cord, p. 878.

Hereditary Ataxia[1] **(Friedreich's Ataxia)**.—As this affection is of a hereditary nature, it seems highly probable that its cause lies in some error of development.

Morbid Anatomy.—In this disease sclerosis of the posterior columns is invariably present, and, in the main, the lesion is similar to that of the ordinary form of posterior spinal sclerosis. The posterior nerve-roots are also affected. In addition to the sclerosis of the posterior columns, marked sclerotic changes in the lateral motor and anterior columns occur; the resulting involvement of the pyramidal tracts causes atrophy of the muscles that are innervated by the diseased nerves. The microscopic changes are the same as in the other scleroses.

Primary lateral sclerosis (primary spastic paraplegia) is characterized by a sclerosis of the pyramidal tracts, both lateral and anterior, but chiefly lateral. The cord presents the macroscopic and microscopic

[1] Gowers, "Lancet," April 12, 1902. Aubertin. "Arch. Gen. de Méd.," 1904, p. 1992. Pic and Bonnamour, "Nouv. iconogr. de la Salpêtrière," 1904, No. 2, p. 127

appearances characteristic of all the sclerotic conditions, and as these peculiarities have been described in connection with the other forms of sclerosis, it would be useless to repeat them here. The degeneration seems to be primary and limited to the motor tract. In pure cases the association tracts of the cord are not involved and the anterior cornua are not diseased.

Combined lateral and posterior sclerosis[1] (**ataxic paraplegia**) is a disease closely related to lateral sclerosis, and both affections seem to be produced by the same causes.

Morbid Anatomy.—The cord presents the combined lesions of posterior and lateral scleroses. The lesion of the posterior columns, however, is not identical with that found in the ordinary posterior spinal sclerosis, differing principally in the fact that the disease is not usually so intense, and that the dorsal region suffers more than the lumbar. The lesions in the lateral and anterior columns are quite variable, both in extent and position, but, on the whole, resemble those of lateral sclerosis.

Tumors of the Cord.[2]—*Gliomata* are the most frequent tumors of the cord. They present the same gross and microscopic appearances that characterize similar growths affecting the brain. The effects produced depend, of course, on the size and situation of the tumor. *Gliosarcomata* also occur. Several different varieties of *sarcomata* are occasionally seen. Secondary *carcinomata* and *sarcomata* are sometimes found. *Tuberculous* lesions and *gummata* may occur, but are quite rare. *Cysts* due to both the *echinococcus* and *cysticercus* have been observed.

Syringomyelia.[3]—This affection is characterized by the formation of one or more cavities in the cord. The most frequent seat is in the cervical enlargement, in the vicinity of the central canal, and in the gray substance of the posterior commissure. From this point of origin the cavity usually extends into the cornua. The white matter is generally spared, but becomes involved when the destruction of the cornua is more or less complete. The cavity is filled with a liquid analogous to the cerebrospinal fluid. According to some writers, the excavation results from disintegration of an embryonic tumor composed of neuroglia. Indeed, in a number of cases the cavity is surrounded by a mass resembling gliomatous tissue. The medullary fissure around the excavation is compressed and the cord flattened; the posterior and the lateral tracts usually undergo changes. As a constant clinical phenomenon should be mentioned the sensory dissociation which consists of loss of the sense of pain and temperature and preservation of touch. Pain and temperature sense are conducted by Gowers's tract, which comes from the opposite side of the cord and traverses the white commissure. As the cavity in syringomyelia is around the center of the cord, the fibers of Gowers's

[1] Russell, "Clinical Record" (London), Dec. 20, 1899. Crouzon, "Des Scleroses combinees de la Moelle," Paris, 1904.

[2] Hunter, "Brain," Summer, 1902, p. 226. Collins, "Med. Record," December 6, 1902. Tytler and Williamson, "Brit. Med. Jour.," Feb. 7, 1903, p. 301. Cushing, "Annals of Surgery," June, 1904, p. 934.

[3] Zappert, "Wien. klin. Woch.," Oct. 10, 1901. Fleger, "Wien. klin. Woch.," 1902, Nos. 32, 33 and 34. Kienböck, "Jahrb. f. Psych.," 1902, xxi, p. 50. Bressaud, "Arch. Gen. de Méd.," 1903, No. 52. Gowers, "Lancet," Oct. 10, 1903, p. 993. Thomas and Hauser, "Nouv., Iconogr. de la Salpêtrière," 1904, tome xvii, No. 6, p. 376.

tract are always involved. Under the microscope, besides the gliomatous tissue can be seen debris of the disorganized nervous tissue in the immediate vicinity of the cavity, cells of the cornua, denuded axis-cylinders, and amyloid bodies. An important feature of syringomyelia is the secondary degeneration (see pp. 860 and 882) of various tracts which depend upon the seat of the lesion. The meninges are usually intact.

THE NERVES.

Nothing of importance is known of the minor *circulatory disturbances* in nerves. It is probable that the amount of blood within them is influenced in a greater or less degree by the same causes that produce like results in the central nervous system; the quantity of blood would certainly be increased in the active stages of inflammation.

Hemorrhage into the nerves results from injury, and is sometimes seen in infectious diseases, especially the hemorrhagic septicemias. A considerable part of the nerve may be infiltrated by blood which later undergoes alterations similar to those described when discussing hematomyelia (p. 880).

Infiltrations of nerves are infrequent and of little clinical importance; after injury and following infection, calcareous matter is occasionally deposited within the nerve-trunk. Fatty infiltration is infrequent; irregular collections of fat are sometimes found in the larger nerves, and such fatty masses may be of sufficient size to justify the name lipoma. After degenerations and necroses the residual tissue of the nerve may contain pigment.

Degeneration of the nerves[1] follows any lesion which deprives the fiber of its connection with the ganglion cell (see Wallerian degeneration, p. 861). Diseases of the ganglion cell terminating in its destruction are followed by degenerative changes in the fiber to which the cells give origin. (See anterior poliomyelitis, acute and chronic, pp. 883 and 884.) Gradually applied pressure, as by growing tumors, cysts, and inflammatory processes, also induces degeneration of the myelin and axis-cylinder. The metamorphoses resulting from infections and toxic conditions are usually classed with the inflammations of nerves.

Inflammation of the nerves is called **neuritis.** It may be *acute* or *chronic;* in some cases a single nerve-trunk is involved, and in other instances a large number of the nerves are affected, and the condition is called **polyneuritis.** When the inflammation tends to extend from the point of origin toward the nerve-centers, it is termed **ascending neuritis,** and when the lesion travels in the opposite direction, **descending neuritis.**

Inflammation of the nerves may result from a large number of causes, all of which can not be enumerated in the space available. Certain of these etiologic factors operate locally; among this group must be included trauma, extension of inflammation from contiguous tissues, and the results of cold and exposure when manifested in a single nerve-trunk. The internal causes are toxic substances affecting the nerve from the circulating blood and lymph. These poisons may be of metabolic origin, and with this group are included those giving rise to the

[1] Kattwinkel and Kerschensteiner, "Lubarsch and Ostertag's Ergebnisse der allg. Path. u. path. Anat.," Neunter Jahrg., I Abt. 1903, p. 7.

neuritis occurring in gout, diabetes, or uremia. Of the inflammations of nerves due to poisons introduced from without, those resulting from ptomain and other types of food poisoning, alcohol, and the acute and chronic intoxications by such metals as arsenic, copper, and mercury may be cited. A definite group of nerve inflammations accompany certain in-

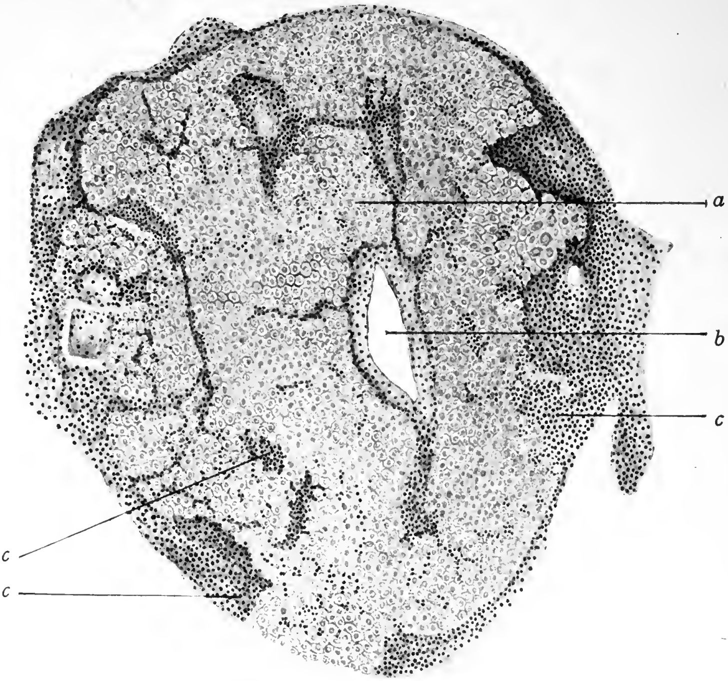


FIG 420.—NERVE. ACUTE INTERSTITIAL NEURITIS.
Fixed in Heidenhain's solution; stained with toluidin-blue and eosin. *a*. Normal nerve-fibers. *b*. Blood-vessels. *c, c, c*. Collections of lymphoid cells between the nerve-fibers.

fectious diseases.[1] The nerve lesion of anesthetic leprosy (p. 158) is a leprous neuritis. In pyemia, septicemia and other mycoses of the blood, inflammations of the nerves are sometimes observed. **Beri beri**[2] or *kakke*

[1] For a study of diphtheric neuritis, see Aubertin, "Centrabl. f. Kinderheilk.," vol. ix, No. 3; Babonneux, Thèse Fac. de Méd. Paris, 1904; Rolleston, "Practitioner," November, 1904, p. 597; Butler, "Med. News," Jan. 21, 1905, p. 117. For typhoid neuritis consult McCrea, "Amer. Med.," Sept. 26, 1903, p. 503; Pascoletti, "Gaz. degli Osped. e. delle Clin.," March, 1904; Keen, "Surgical Complications and Sequels of Typhoid Fever," 1898. Tuberculous neuritis, Clément, "Acad. des Science," Feb. 6, 1905; "La Sem. Méd.," Feb. 15, 1905, p. 79. Syphilitic neuritis, Cestan, "Nouveau Iconogr. de la Salpêtrière," 1900, xiii, p. 153. Malarial neuritis, Luzzatto, "Berl. klin. Woch.," April 28, 1902, p. 375. Neuritis following pertussis, Eshner, "Jour. Amer. Med. Assoc.," Jan. 10, 1903, p. 88; also Valentin, Thèse de Paris, 1903. Neuritis following mumps, Zahorsky, "Interstate Med. Jour.," Sept., 1903, also Dopter, "Gaz. des Hôp.," Aug. 2, 1904, p. 857. Influenza, Mix, "Medicine," May, 1904.

[2] Luce, "Arch. f. Schiffs-u. Tropenhygiene," July, 1902. Wright and McGill, "Brain," Winter, 1903. Uchermann, "Zentralbl. f. inn. Med.," June 18, 1904.

is a form of endemic, sometimes epidemic, multiple neuritis observed especially in China, Japan, certain parts of India, the Philippine Islands, and other tropical and subtropical countries. The most common form of multiple neuritis is that caused by alcohol; the condition may, however, be the result of poisons other than alcohol and of any of the infective diseases.

Morbid Anatomy.—On examination the inflamed nerve—especially if the process be acute and of a decided character—is found more or less reddened and swollen. At a later stage the nerve may shrink to a certain extent, owing to the formation of fibrous tissue. On microscopic examination the nerve presents changes the peculiar character of which depends upon whether the fibers or the interstitial structures are most affected; the former variety is called *parenchymatous neuritis;* the latter, *interstitial neuritis.* In localized neuritis the interstitial changes are usually pronounced, while in the multiple forms the myelin and axis-cylinder (parenchyma) are primarily involved. Either variety, if pronounced, ultimately gives rise to the other.

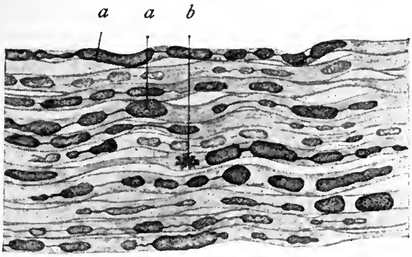


FIG. 421.—LONGITUDINAL SECTION OF THE MUSCULOSPIRAL NERVE, REMOVED FROM A MAN WHO DIED AS A RESULT OF ALCOHOLIC MULTIPLE NEURITIS.
Section hardened in Müller's solution; stained by Weigert's new hematoxylin method. *a, a.* Showing remains of myelin sheaths of nerves. *b.* Compound granule corpuscles. (Queen obj., ¼-in.: oc. B.)

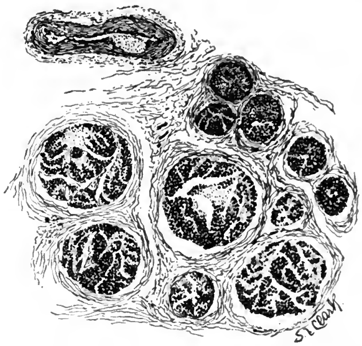


FIG. 422.—NEURITIS DUE TO CHRONIC LEAD INTOXICATION.—(*Gordon*).
Section of musculospiral nerve. Weigert's stain; the degenerated fibers are unstained. The vessel in the left upper corner of the illustration contains a nodule of arteriosclerosis.

In the acute stages the interstitial form shows under the microscope fullness of the blood-vessels, more or less swelling of the tissue, and an accumulation of leukocytes in the part; these cells are polymorphonuclear if the process be suppurative, and lymphoid if otherwise. Slight extravasation of blood may occur. These changes are usually localized along the course of the track affected, though they may be diffused with a certain degree of uniformity. If the inflammation be severe, the nerve-fibers begin to show changes that may be either inflammatory or degenerative, it is difficult to say which; the latter view is generally accepted. The alteration first observed is a breaking up of the myelin into irregular masses that may or may not be connected with one another by thin filaments of the same substance. If prepared by Marchi's method (p. 853), microscopic sections show areas of fatty change. The axis-

Holst, "Norsk Mag. for Lægevidenskaben," Oct., 1904. Fajardo, "Arch. f. Schiffs-u. Tropenhyg.," Oct., 1904, Bd. viii, No. 10. Durham, "Jour. of Hyg.," Jan., 1904, p. 112.

cylinders are usually interrupted at the points where the myelin is divided. The nuclei of the nerve-sheath increase in number. Gradually, the myelin further degenerates, and, in many parts of the nerve-fibers, entirely disappears; when this occurs, the primitive sheath collapses, and ultimately the entire nerve may be destroyed, being replaced by fibrous tissue. As the process becomes older compound granule cells make their appearance within and around the fibers. If the inflammatory phenomena be slight, the nerve-fibers do not suffer to so great a degree. In the chronic forms the fibrous tissue is usually greatly increased; this condition is commonly observed in the peripheral

FIG. 423.—CHRONIC INTERSTITIAL NEURITIS, SHOWING DEGENERATION IN SOME OF THE NERVE-FIBERS.—(*Gordon.*)
The interstitial tissue is everywhere increased and the perineurium thickened. The patient had arteriosclerosis

nerves particularly of the aged, and is probably the result of arteriosclerosis.

Whether the neuritis be primary or secondary the similar alterations are observed within the nerve-fibers involved. Degenerative changes occur in the muscles supplied by the diseased nerves. The fibers lose their striation, become granular, fragmented and eventually fatty; the nuclei of the sarcolemma and interstitial tissue increase in number, and finally absorption of the degenerated and necrotic elements leaves the affected muscles extremely wasted. The condition constitutes one form of secondary degeneration of muscle (p. 788).

Degenerative changes in the nerve-trunk follow various spinal and many cerebral lesions. The structural alterations, occurring in the nerves, differ in no way from those described in connection with

what is called inflammation. The interstitial changes are, of course but slight in these cases.

Regeneration of Nerves.[1]—If a nerve be divided, that part distal to the solution in continuity undergoes degeneration (see Secondary Degeneration, p. 860). Regenerative efforts are usually manifest within a few days following the receipt of the injury. With regard to the essential nature of the changes by which restitution is accomplished, two views have generally been held. According to one of these, the regeneration progresses from the center toward the periphery, and is practically entirely dependent upon the projection of new fibers from the central segments. Those who hold to this method of regeneration no longer deny that the neurolemma of the young fibers is derived from pre-existing elements of the distal segment. Ballance and Stewart have reviewed the older observations and conducted an elaborate series of experiments which seem to establish the peripheral theory of nerve regeneration. During the first eighteen hours following the injury, leukocytes invade the distal fragment and also the proximal segment, the latter in the vicinity of the wound only. By the third day the leukocytes have almost disappeared and large oval and vesicular connective-tissue cells become numerous throughout the distal segment. These elements, assisted by the proliferated neurolemma cells, remove the myelin apparently by phagocytosis which begins about the fourth day and persists for several weeks. By the second or third day the neurolemma cells begin proliferation, which is at first patchy along the course of the distal segment, but later becomes uniform. By the second or third week these elongated cells form columns, and by the fourth week the production of nerve-fibers by the neurolemma cell is evident. Within twenty-four hours following the injury a primitive end-bulb is formed on the distal extremity of the proximal segment and is due to curling of the divided fibers. After preliminary degeneration the changes observed are identical with those occurring in the distal fragment. The establishment of continuity between the two structures is accomplished by neurolemma cells extending across the defect and eventually producing both axis-cylinders and medullary sheaths.

Tumors of Nerves.[2]—The most frequent neoplasms affecting the nerves are the so-called **pseudoneuromata,** of which *fibroneuromata* are the most common, although **myxoneuromata** are occasionally observed. The condition called **neurofibromatosis** (p. 342) is manifested by numer-

[1] Ballance and Stewart, "The Healing of Nerves," 1901. Durante, "Nouv. iconogr. de la Salpêtrière," 1903, No. 6. Henriksen, "Lancet," April 11, 1903, p. 1015. Kennedy, "Brit. Med. Jour.," Sept. 24, 1904, p. 729. Powers, "Annals of Surgery," Nov., 1904, p. 633. Langley and Anderson, "Jour. of Physiol.," Aug. 22, 1904. Schütte, "Centralbl. f. allg. Path. u. path. Anat.," Nov. 30, 1905 Spiller and Frazier, "Univ. of Penna. Med. Bull.," June, 1903.

[2] See Neuromata, p. 320; also Neurofibromatosis, p. 342, and Tumors of the Brain, p. 875. Anthony, "Jour. Amer. Med. Assoc.," June 13, 1903, p. 1630. Fränkel and Hunt, "Med. Record," June 13, 1903, p. 925. Thomas, "Johns Hopkins Hosp. Bull.," Aug., 1903, p. 204. Cestan, "Revue Neurolog.," Aug. 15, 1903, p. 745. Durante, "Nouv. iconogr. de la Salpêtrière," Nov and Dec., 1903. Noyes, "Jour of Path. and Bact.," Dec., 1903, p. 240. Be ger, "Arch. Gen. de Méd.," 1904, p. 1367. Fabris, "Arch. per le sc. Méd.," 1904, fasc. ii. Rudler, "Nouv. iconogr. de la Salpêtrière," May and June, 1904, vol. 17. Hulst, "Psychiatrische und Neurologische Bladen," 1904, May and June, No. 3. Bourcy and Laignel-Lavastine, "Soc. Méd. des Hôp.," Jan. 13, 1905. Meek, "Boston Med. and Surg. Jour.," March 30, 1905.

ous tumors distributed in the peripheral nerves. *Amputation neuromata* commonly develop on the ends of nerves in amputated extremities; Durante has reported a case in which neoplasms of this type developed on the distal end of the proximal segment and on the proximal end of the distal fragment. The *tubercula dolorosa* or painful subcutaneous tubercle is usually a fibroma surrounding a small nerve filament. Carcinoma and sarcoma sometimes involve nerves distributed in the tissue invaded by the new growth; as a rule, however, these structures escape infiltration.

PART IV.

APPENDIX.

GENERAL LABORATORY TECHNIC.

PART IV (APPENDIX).—GENERAL LABORATORY TECHNIC.

CHAPTER I.

BACTERIOLOGIC TECHNIC.[1]

In order satisfactorily to study microorganisms we must be able to secure, and if possible to maintain, *pure cultures*, a term to be explained later. The soil upon which bacteria are grown is called a *culture medium*. The soils, or culture media, are classed under two heads—the **natural** and the **artificial**; of each of these we have two kinds, the *fluid* and the *solid*.

Natural Culture Media.—*Fluid:* Blood-serum, milk, urine, aqua coca, hydrocele fluid, eggs or egg-albumen, etc. *Solid:* Blood-serum, eggs, potatoes and other tubers, and fruits.

Blood-serum is the most valuable of all natural culture media, and may be used either in the fluid or in the solid state. The serum may be obtained from any of the lower animals, though that of the calf or ox is preferred. The blood is collected in clean jars at the time of slaughtering; a gallon fruit or museum jar answers the purpose. If the blood is passed directly from an artery into a sterilized jar, it will remain sterile. The freshly drawn blood is allowed to coagulate in the sterile receiver; it is then removed to the laboratory. A sterile glass rod is passed around the outside of the clot, between the coagulum and the jar, in order to detach the fibrin from the jar and to permit the clot to contract. The jar is then placed on ice. In from twelve to twenty-four hours the clot will have separated, and the serum may be drawn off with a sterile siphon. If it is clear, it may at once be placed in tubes; if there be much suspended coloring-matter,—red blood-cells,—it may be set in the ice-box for sedimentation, after which the clear supernatant fluid may be poured into the culture containers. If this operation be conducted with proper care, the serum should not require sterilization, and can be used in its fluid state. In order to avoid infection the greatest care must be taken in every stage of preparation. Containers, pipets, instruments, hands, etc., must be sterilized with the utmost care and maintained in an aseptic condition. It is hardly necessary to say that such extreme care can rarely be taken, so that the Councilman-Mallory method (given below) has practically superseded this more tedious process. If, however, a solid medium is wanted, the serum is sterilized and "set" by heating.

In order to sterilize blood-serum it must be heated one hour each day for four days; as high temperatures cause coagulation of the albumin, the heat had best not exceed 65° C. It is rendered solid by

[1] For more detailed consideration of Bacteriologic Technic see works referred to in foot-note 1, p. 81.

gradually raising the temperature until coagulation is just sufficient to solidify; at this stage it is slightly opalescent, of a yellowish straw color, and easily penetrated by a needle. The temperature necessary for solidification rarely exceeds 70° C. Councilman and Mallory avoid the foregoing tedious process in the following manner:

Blood is collected in a clean jar and permitted to coagulate; the fibrin is detached, as already directed. The more or less clear serum is then siphoned off. The small amount of blood present does not interfere with the subsequent handling or with the use of the medium for culture purposes. Previously sterilized test-tubes, prepared as directed under Culture Containers (p. 903), are at once charged with the fresh serum and placed in a slanting position in a dry-air sterilizer, the temperature of which is raised to 80° or 90° C. The heating must be gradual, and must not exceed the temperature given. As soon as solidification is complete the serum is transferred to a steam sterilizer (the tubes being placed on end), and sterilized at 100° C. for thirty minutes each day for three successive days.

Löffler's blood-serum mixture contains:

Bouillon containing one per cent. glucose,	1 part.
Blood-serum,	3 parts.

The two are mixed, placed in the tubes, and sterilized as directed for blood-serum. The medium is especially useful for the Bacillus diphtheriæ, but may be used for almost any organism, and is, taken all in all, one of the best all-round media found in the laboratory. The advantages offered by the Councilman-Mallory method may be utilized in the preparation of this medium. The formula and preparation of bouillon are given with artificial culture media (p. 900).

For a number of purposes, and especially for cultures of gonococci, **human serum** is useful; it may be obtained from blood collected by phlebotomy, or blood expressed from the human placenta. From whole blood it is prepared as already directed for animal serum. Ordinarily, transudates or exudates in the large serous cavities are collected at autopsy or operation, distributed in tubes, sterilized, and if necessary coagulated in the same manner as separated serum. All fluids withdrawn from serous cavities do not contain sufficient albumin to solidify properly by heat; such fluids must be used in a liquid form or solidified by the addition of gelatin or agar.

Wertheim's medium is prepared by adding one part of sterile, freshly drawn human blood or blood-serum, to two parts of liquefied agar at 45° C.; the tubes are then slanted and the medium allowed to solidify. **Blood-smeared agar** is especially useful for the cultivation of the influenza bacillus; it is prepared by smearing a few drops of freshly drawn sterile blood on the surface of agar slants which should be incubated a few days to assure sterility.

Fresh **milk** normally is alkaline; if acid, suspicion must be entertained as to its freshness. For use as a culture medium the cream should be removed by centrifugalization; or if the milk be placed in a large container, steamed for fifteen to twenty minutes, and left in an ice-box for twenty-four hours, the cream will rise to the surface and may be siphoned off. The milk is then filled into tubes and sterilized, preferably by the fractional method. For the purpose of determining the

production of acid[1] or alkali by bacteria, litmus milk is used. This is prepared by adding to each liter of milk 100 c.c. to 150 c.c. of a watery solution of litmus prepared by dissolving 6 grams of purified litmus in 1000 c.c. of water, using heat if necessary, followed by filtration. The resulting mixture is distributed into tubes and further sterilized by the fractional method. Some bacteria coagulate the casein, others peptonize it.

While they are useful, the employment of urine, aqua coca, and hydrocele fluid is not general.

Boiled **potato** affords a splendid culture medium for the growth of many bacteria. Potato used as a culture medium is first thoroughly washed in water to remove dirt, then in a 1 : 1000 solution of corrosive sublimate, followed by sterilized water for ten or fifteen minutes to remove the mercury. The potato is then cut into slices. With an apple-corer pieces of the proper size are cut from the slices, slipped into sterilized test-tubes, and a small quantity of distilled water is added to prevent rapid drying after sterilization. Instead of using an apple-corer, the potato may be cut into a long, pyramidal piece resembling a gigantic exclamation point. The small end of the pyramid should be long, and project downward into the water at the bottom of the tube, thus preventing desiccation of the upper part of the piece, upon which the culture will be made. The culture tubes containing pieces are now sterilized by placing them in an autoclave for from twenty to twenty-five minutes; or, by fractional sterilization, for an hour a day, for from three to five days, in a steam sterilizer. They are now ready for inoculation.

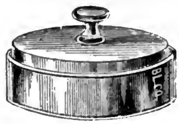


FIG. 424.—MOIST CHAMBER FOR POTATO CULTURE.

To use this dish, or any similar chamber, for potato cultures, the dish is sterilized in a hot-air sterilizer and allowed to cool. In the bottom is placed a blotter, moistened with a 1 : 1000 solution of corrosive sublimate. The potato is cleaned as described in the text, and is sterilized whole; a thin knife, such as is shown on page 18, is also sterilized; the worker thoroughly disinfects his hands and takes the sterile potato in the left hand and the sterile knife in the right hand; the potato is then incised in its longest diameter, and, without separating the two halves, an assistant raises the upper half of the dish by the knob while the potato is quickly placed on the sterile blotter, the two halves being separated so that the freshly incised surface of each half is turned upward; the lid is now quickly replaced. If no growth occurs on the potato in three or four days, it may be considered sterile, and may be inoculated.

Sterilized eggs are occasionally used for the cultivation of anaerobic bacteria. The eggs are thoroughly sterilized at a low temperature, as already directed for blood-serum, a point in the shell is carefully penetrated with a sterile borer, the egg is inoculated, and the puncture sealed with wax. Occasionally, sterilization may not be necessary; but without it incubation can not well be applied, as the chick develops too rapidly. After inoculation the egg may be dipped in hot paraffin, which, on cooling, forms an air-tight covering.

Artificial Culture Media.[2]—*Fluid:* Inorganic solutions, organic mixtures, bouillon, and vegetable and animal infusions. *Solid:* Bouillon, milk, etc., solidified by the addition of gelatin, agar-agar, or gelatin and agar-agar. To cultivate certain bacteria,—the tubercle bacillus, for instance,—it may be necessary to add glycerin to the medium.

[1] For method of estimating the production of acid by bacteria in culture see Hanna, "Jour. of Path.," October, 1898, p. 267.

[2] For the preparation of salt-free culture-media see Taylor, "Jour of Experimental Med.," Feb. 25, 1905, p. 111.

The most useful artificial culture media are infusions of beef and mutton containing a small quantity of peptone. Most of the bacteria develop quite readily in such media. The stock culture media is Koch's **alkaline-beef-peptone bouillon.** For ease and rapidity of preparation the following is recommended: Take an ordinary farina boiler (agate-ware is best), and fill the outside kettle with sufficient water to inclose the inside can; into the latter put one liter of water, which had best be distilled; with a diamond or file, mark on the side of the can the height of the fluid. Marks made on the side of the container are often difficult to find or to differentiate from other scratches, particularly when the can is more or less filled with steam and boiling fluids. An equally efficient and somewhat simpler method is to mark upon a glass rod the depth of the fluid, subsequently maintaining the same depth by the addition of water. Obtain 0.5 of a kilogram of finely chopped lean beef from which the fat has been carefully removed; add this to the water, a little at a time, stirring constantly so as to make sure that every piece

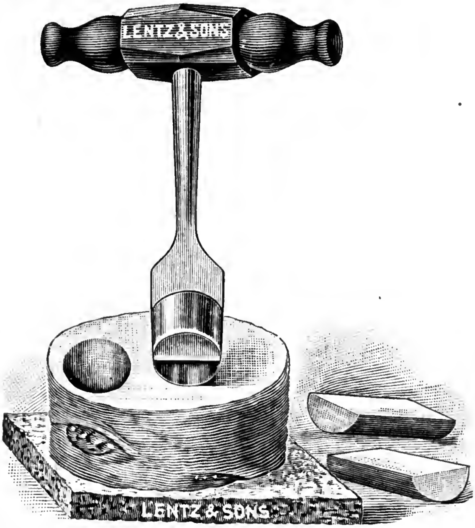


FIG. 425.—INSTRUMENT FOR CUTTING PLUGS OF POTATO FOR POTATO CULTURES.

The cut plugs are washed in water and pushed down into test-tubes into which the potato segment fits closely. Enough water is added to come just up to the lower end of the plug. The tubes are then sterilized as directed in the text.

FIG. 426.—AGATE-WARE WATER-BATH (FARINA KETTLE).

Used in making culture media, and convenient for many purposes about the laboratory; the capacity should be about 1000 c.c. for inside boiler.

of the meat is well penetrated. The original directions required that this mixture macerate for twelve hours before proceeding with the next step. Usually maceration is unnecessary, although some workers apparently always macerate for twelve or twenty-four hours, as originally advised. Whether macerated or not, the next step is to add the peptone and salt. Take ten grams of Witte's dried beef-peptone and five grams of salt (sodium chlorid), and mix them thoroughly in a mortar or teacup; add just enough water to rub the mixed powders into a thin paste, which is now added to the meat-and-water mixture in the farina kettle and thoroughly stirred into the mass. The water in the outside kettle is now brought to a boil, during which time the mixture in the inside kettle has been frequently stirred. As soon as the albumin begins to coagulate the stirring is stopped, and when coagulation is fairly ad-

vanced—after fifteen or twenty minutes' boiling—the inside kettle is removed from its surrounding water-bath and its contents boiled over the flame, care being taken that it does not boil over. The meat and coagulated albumin collect into a rather dense mass, which should be broken up, so that the interior may be fully penetrated by the boiling fluid in order to extract the salts contained in the meat. After thirty minutes' boiling the mass is removed from the flame and strained through flannel. The water lost by evaporation must be made up by pouring enough cold water over the meat in the strainer to bring the filtrate to one liter. If any fat is seen over the surface of the fluid, as much as possible is removed with a spoon or by gently touching it with paper or a clean cloth. The filtrate is usually clear, and, if not, it must be filtered. Tested with an indicator, this fluid will be found acid, and must be made neutral or faintly alkaline. This is best done by adding, drop by drop, a ten per cent. solution of caustic soda (sodium hydroxid). The best indicator is a phenolphthalein solution, made by dissolving one gram of phenolphthalein in 1000 c.c. of fifty per cent. alcohol. A watch-glass containing about 1 c.c. of this solution is placed conveniently, and into this a drop of the bouillon is mixed, a different watch-glass being used for each drop; as soon as alkalinity is reached, the indicator turns a bright rose-color, which, while distinct, should be faint. Litmus paper may be used for the same purpose but is less delicate, although sufficiently accurate for routine work. With the disappearance of acidity the bouillon becomes faintly cloudy, the salts and albumins, insoluble in an alkaline fluid, precipitating. To complete the formation of this precipitate the fluid is thoroughly boiled for at least thirty minutes, and then filtered. It is advisable, when a perfectly clear fluid is absolutely essential, to cool the medium, filter, reboil, and again filter; this is rarely done, and is useless except that it assures the medium remaining clear; after each boiling, and before finally filling the culture vessels, the alkalinity of the fluid must be tested, for, in some inexplicable manner, a fluid previously known to have been neutral, or even alkaline, may become acid. When finished, the resulting fluid is known as neutral-, alkaline-, or acid-beef-peptone bouillon, the first word of the name always indicating the reaction. When intended for the cultivation of tubercle bacilli, glycerol (glycerin) is added (the amount commonly employed is six per cent.)—60 gm. of the glycerol, which must be weighed and not measured, to 1000 c.c. of the bouillon. It is now known as alkaline-glycerin-beef-peptone bouillon.

Instead of the 0.5 of a kilogram of beef used in the above, two grams of meat extract (Liebig's or Armour's) may be substituted. The preparation is practically the same, except, of course, the flannel filter is not needed, and, as the meat salts are exceedingly difficult to remove, filtering while hot, and again when cold, may require frequent repetition to secure a perfectly clear fluid. Media prepared with an extract are not so satisfactory as those made from the beef direct. Streptococci grow indifferently or not at all upon media prepared from commercial extract.

When it is desired to render the foregoing solid, gelatin or agar, or both combined, may be used.

Beef-peptone-gelatin.—To 1000 c.c. of cold bouillon add 100 gm. of gelatin ("gold-leaf," in sheets), torn or cut into fragments; macerate for fifteen or twenty minutes, until the gelatin swells up and becomes

flaccid; it is then easily dissolved by gently heating in a water-bath; by the time it has reached a temperature that will not scald the fingers the gelatin will be dissolved. It is now removed from the water-bath and cooled until the fingers can be comfortably held in it for some time —about 50° C. or lower. When the gelatin is thoroughly dissolved, the fluid will require realkalinization; as gelatin is constantly acid, the reaction of the previously alkaline bouillon is changed. The alkalinization must be most carefully done, otherwise the gelatin may fail to solidify when finished. Again, one must be sure that all the gelatin is dissolved before alkalinization or, later, the reaction may be found acid. It must be but *faintly* alkaline. If by accident the fluid be made too alkaline, a few drops of dilute acetic acid will correct the error. When the reaction is satisfactory, the white and finely broken shell of two eggs is thoroughly mixed with the gelatin; this is heated to the boiling-point in a water-bath, followed by boiling over the naked flame (which is best distributed by wire gauze) for at least half an hour; the water lost by evaporation is made up, and enough of the mixture filtered to half fill a good-sized test-tube; this is boiled repeatedly for several minutes, to see that all the albumin is coagulated, the reaction as desired, and that the gelatin remains clear; if so, the remainder is filtered and placed in test-tubes. When properly made, gelatin is the clearest solid medium at present attainable. It is liquid at temperatures above 22° C., and can not, for this reason, be incubated. As some bacteria liquefy gelatin and others do not, it constitutes a test culture medium of the greatest value.

Beef-peptone-agar.—Agar-agar is a gelatinizing agent derived from a Japanese seaweed. It is used for making culture media solid in the following manner: To 1000 c.c. of bouillon add ten grams of the agar threads cut into fragments not over two centimeters in length; place at once to boil over the naked flame, stirring frequently to prevent burning and the threads adhering to the bottom of the pan. It usually requires about an hour to secure perfect solution, without which filtration is impossible. Longer boiling does no harm, the quantity of the medium being maintained by adding, from time to time, enough water to compensate for that lost by evaporation. When fully dissolved, it is filtered. As it filters with much more difficulty than gelatin, and as the same precautions are necessary, I have deferred the description until now. An efficient, heavy, preferably already folded filter (machine-folded filters are by far the best) is carefully opened and adjusted in the funnel; then, with the greatest care, thoroughly moistened with boiling water; a moment is allowed for the contraction of the filter, which always takes place; it is then again moistened with boiling water, the excess poured off, and the agar or gelatin poured down a glass rod on to the *side* of the filter—*not* into the center and never rapidly, as either may break the paper. In the case of agar it is best to have it boiling and add but 250 c.c. or less to the filter at one time, keeping the remainder hot in the water-bath and heating to boiling just before pouring into the filter.[1] Gelatin can not be boiled very long or it may fail to gelatinize; with agar this danger is not present. Gelatin burns to the pan unless carefully watched; agar may do so, but less frequently. Gelatin should always be cleared

[1] For other methods of clarifying agar see Alleger, "Jour. of Applied Microscopy," January, 1898; also Carter, "Jour. of Applied Microscopy," April, 1898.

by an egg; agar may be, but does not require it. Agar solidifies at about 42° C., and melts only near the boiling-point; it is not so clear as gelatin, but, as it can be incubated, has many advantages. It remains solid when prepared with glycerin bouillon, which gelatin does not always do.

Urine agar, which is particularly useful for the cultivation of the gonococcus, is made by using urine instead of bouillon. The urine is neutralized or rendered faintly alkaline, or it may be used in its acid condition. One per cent. of peptone and 0.5 per cent. of salt may be added, although this is not ordinarily necessary. After filtration, preliminary boiling, and filtration while hot and again when cold, the agar is added, dissolved, and filtered as already directed. For the preparation of agar media containing blood and blood-serum see page 898.

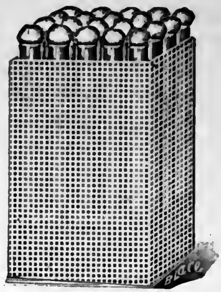


FIG. 427.—TEST-TUBE BASKET MADE OF TINNED METAL FOR HOLDING TEST-TUBES.
These baskets should be 125 by 100 mm., and 150 mm. high.

Culture Containers.—Cultures may be made in bottles, flasks, or test-tubes; the last two are the most used. If perfectly new, a thorough rinsing in clean water will suffice; if the tubes have con-

FIG. 428.—DOUBLE-WALL HOT-AIR STERILIZER, FOR STERILIZING TEST-TUBES, GLASSWARE, AND OTHER LABORATORY APPLIANCES AND INSTRUMENTS.

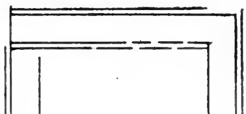


FIG. 429.—DIAGRAM OF INTERIOR OF HOT-AIR STERILIZER.—(*Coplin and Bevan.*)
The construction must be such that a jacket of hot air surrounds the inside chamber, and thereby assures an equal distribution of heat to the interior.

tained cultures, or have in them cultures either growing or dead, they should be placed in the sterilizer for a couple of hours, with the cotton plugs in place; remove from sterilizer, take out the plugs, pour out the contents

of the tubes, and boil one hour in a two per cent. solution of washing soda; wash with test-tube brush and rinse in several changes of clean water; rinse in a one per cent. solution of hydrochloric acid; carry through several changes of water, and dry with bottom upward. When dry, plug with cotton; for this purpose ordinary cotton batting, clean and free from the cotton hulls, is used. Absorbent cotton possesses no advantages. A more or less square or octagonal disc of cotton, about ten centimeters in diameter, has its corners folded into the center so as to make a plug twice as long as the diameter of the tube or the neck of the flask. The plug should fit so tightly that the tube or flask can be lifted safely by the cotton plug, which should enter the mouth to a distance equal to twice the diameter of the tube or the neck of the bottle or flask, and should project at least one centimeter.

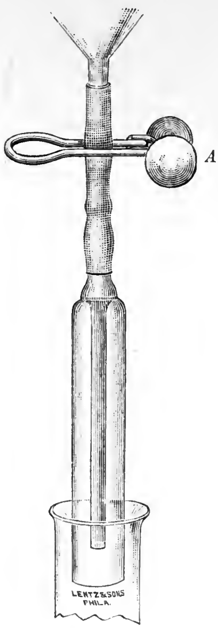


FIG. 430.—TUBE FILLER. Apparatus to be attached to the lower end of a funnel, as shown in the cut, for use in filling test-tubes. The outside glass tube prevents the medium that flows from the inside tube from coming in contact with the mouth of the test-tube during introduction or withdrawal. *A*. Mohr's spring pinch-cock.

The test-tube used for cultures should be of the best Bohemian glass, with a lumen of 13 mm. to 15 mm., and 130 mm. to 150 mm. in length. The best flasks are of the Erlenmeyer form, with a capacity of 100 c.c. Larger sizes, 250 c.c. to 1000 c.c., will be needed for storing media.

After cleaning and plugging, the tubes and flasks are put in the hot-air sterilizer for twenty minutes at 130° C. In the absence of a hot-air sterilizer any cooking oven may be used, leaving the tubes in the oven until the cotton just begins to brown, approximately 140° C. The tubes are now ready to receive the medium. By means of a perforated cork and a short glass tube, a rubber tube ten centimeters long is attached to the tubulature at the bottom of an ordinary percolator or funnel; at the lower end of the rubber tube a second glass tube is connected so that it projects about ten centimeters below the rubber tube; the latter is then collapsed by means of a thumb pinch-cock (Mohr's spring pinch-cock) applied to the rubber tubing between the ends of the two glass tubes. The liquefied medium is poured into the percolator; the test-tubes are then arranged in the baskets at the side of the percolator. A test-tube or flask is grasped by the left hand, preferably by the thumb and index-finger; the cotton is rotated and loosened by means of the thumb and index-finger of the right hand, and removed by grasping the projecting tip between the ring- and little fingers of the right hand; the tube is now carefully slipped over the filling tube from the percolator, *care being taken that no fluid comes in contact with that portion of the tube into which the cotton plug is to go;* relax the pinch-cock and admit to the test-tube or flask the desired quantity; close the pinch-cock, remove the tube, *using the same care to avoid wetting the mouth of the tube*, and reinsert the cotton plug. This is repeated until the desired number of tubes or flasks are filled. If any of the medium remains, it may be run into a flask, sterilized as will be directed later, and preserved

for future use. The amount of medium placed in each tube varies with the medium and the purpose for which it is intended. For some experiments a measured quantity will be needed, but for ordinary purposes the tube should be about half filled with bouillon or gelatin, and with agar to a depth equal to a little more than twice the diameter of the tube. Flasks should never be more than half full when intended for culture, and often very much less will be sufficient.

Sterilization.—The Arnold steam sterilizer or the autoclave is used. If the former is selected, **fractional sterilization** is best, keeping filled tubes in the steam chamber, at 100° C., thirty minutes a day for three successive days; in the intervals between sterilizations they are kept at room-temperature. The object of this is to destroy all organisms in the adult or fully developed stage. It is known that spores are not destroyed by a temperature of 100° C. unless it be very long applied; any spores escaping the heat on the first day are given time to develop by the second day, or, to assure their being killed, a third sterilization is practised. Experience teaches that this is usually sufficient; however, the tubes should be watched for three or four days, and if any of them show a growth, the process should be repeated for all.

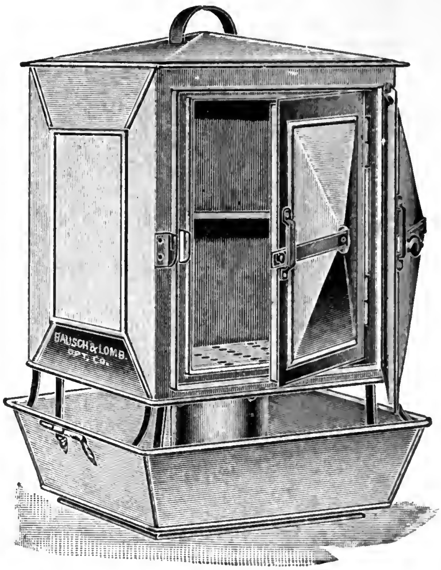


Fig. 431.—Arnold's Steam Sterilizer, Boston Board of Health Form.

This is the most convenient and the best sterilizer for general laboratory purposes.

By means of the autoclave a temperature of 130° C. is obtained in the steam chamber, which, in from twenty to thirty minutes, destroys both fully developed bacteria and their spores; it is of great convenience for bouillon, agar, potatoes, milk, and many other culture media, but can not be used for blood-serum or gelatin. The latter usually fails to gelatinize after being subjected to the high temperature; indeed, gelatin must always be sterilized with the greatest care, as prolonged exposure, even to the temperature of 100° C., should be avoided. Potatoes require prolonged exposure to high temperature, as they usually contain earth organisms difficult to destroy.

Slant Cultures.—In order to increase the surface area of media containing agar or blood-serum, the tubes, while the medium is in a liquid state, are inclined with the mouth just high enough to prevent the agar flowing up to the cotton; when "set," they may be stood on end, as other tubes.

To Prevent Stored Media from Drying.—For this purpose the writer has tried rubber caps, rubber tissue, oiled paper, cork and rubber stoppers, and the paraffin method, none of which seems fully satisfactory.

One of the best methods is to trim the cotton even with the top of the tube, and push it down 0.5 cm. below the tube-lip; take a coin of proper size to drop just inside the lip of the tube; heat the lip of the tube and the body of the tube as far down as the cotton extends, until the cotton is slightly browned, and at the same time heat the coin; drop the coin upon the tube, and, while still warm, seal it to the tube at the margin, using for this purpose a good quality of stationer's sealing-wax. This process is tedious, and is most useful for tubes containing cultures that require long incubation, such as the tubercle bacillus. A much more useful plan, and one almost as efficient, consists in pushing the cotton down, heating the mouth of the tube and inclosed cotton, and placing over the end a disc of quite thick tin-foil, which is evenly folded over the lip of the test-tube. For this purpose commercial tin-foil, which contains a relatively large proportion of lead, may be used, as it is much cheaper than chemically pure tin. Such a cap is easily removed and replaced. It offers all the advantages of rubber, and can, if sufficiently heavy, be readily sterilized.

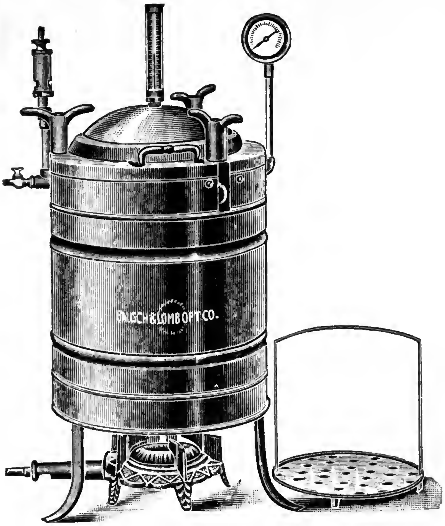


Fig. 432.—Autoclave, or Digestor, Used for Sterilizing by Steam Under Pressure.

The lid is held in place by three winged nuts, which are thrown down to the side in order to raise the lid. The solid copper chamber on the inside has placed in it two liters of water, and the material to be sterilized is placed upon the tray with perforated bottom shown at the side of the cut; this is then placed inside of the autoclave, and the lid is closed down and secured by the winged nuts; the gas is now lighted and the heat applied until steam escapes from the small cock at the left, which is then closed. The pressure within the apparatus now rises until the safety-valve, which may be set at any pressure, blows off. Sterilization by this means may be secured, at temperatures ranging from 100° C. to 140° C., in from twenty to forty minutes.

Dunham's Peptone Solution.—Rub up in a mortar five grams of salt and ten grams of peptone, with enough water to make a paste; finally, dilute to 1000 c.c., boil, and filter. As a rule, the filtrate is neutral or alkaline; in either case, after sterilizing as already described for bouillon, it is ready for use.

For plating it is always best to have on hand a number of tubes of gelatin and agar, each tube two-thirds full.

Pure Cultures.—A pure culture is one containing the progeny of a single germ; for example, a pure culture of the tubercle bacillus must contain no other germ. When two kinds of bacteria are growing together, the growth is said to be a *mixed culture*. Under nearly all conditions various organisms are found together, and in order to separate them we must resort to **plating.** The object to be attained is the separation of each germ, in order to enable it to develop a colony by itself; so that, if the original mixture contained three kinds of bacteria, we may obtain three kinds of colonies, and from these obtain cultures which have but the one variety—that is, a pure culture of each.

Bottle Plates.—Any strong, clear, flat-sided bottle will do. The

capacity should be about 500 c.c.; clean, plug with cotton, and sterilize in hot-air sterilizer; charge with gelatin or agar, usually about twenty cubic centimeters. Sterilize as already directed for culture media, and set the bottle aside until wanted for plating; to prevent the medium from drying, the cotton may be pushed downward in the neck so as to admit a short rubber stopper, or the neck and lip may be covered with tin-foil as already directed. As a rule, the bottle will be used within one month, during which time it should not become dry. When ready for use, at least three bottles will be needed. Liquefy the medium in the sterilizer or water-bath; cool to 50° C. or below, inoculate the first bottle with a small loopful of the mixed culture or suspected material, as pus or blood, replace the cotton plug, and shake, to thoroughly mix; inoculate the second bottle by carrying a loopful from the first to the second, replace the plug, and shake; and in the same manner inoculate a third bottle from the second, and shake as before. Lay the three bottles on the flat side; the medium will spread out and cover the side of the bottle; label the three bottles *a*, *b*, and *c*, the first being *a*.

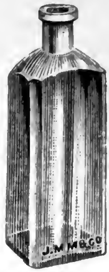


Fig. 433.—Blake Bottle, Used for Bottle Plates.—(*Coplin and Bevan.*)

Petri Dish Plates.—Three or more test-tubes containing sterile agar-agar or gelatin, filled to within an inch or so of the cotton, as already directed, are placed in a water-bath or a sterilizer and the contained medium liquefied; while this is in progress an equal number of Petri dishes are sterilized in the hot-air chamber and allowed to cool. The liquefied medium is cooled to below 50° C. A tube is inoculated with the material to be plated, as directed for bottles; from the first tube a second is inoculated, and from the second a third, and so on, each tube having the medium thoroughly mixed by using the inoculating needle as a stirrer. Remove the cotton from the first tube and pass the lip of the tube through the flame; raise the lid of a sterile Petri dish just enough to get the mouth of the tube under it, and quickly pour the contents of the tube into the dish, which is then gently tilted from side to side in order to distribute the medium uniformly. A second dish receives in the same way the contents of the second tube, and so on, through as many tubes as may be desired. The plates are labeled as directed for the bottles.

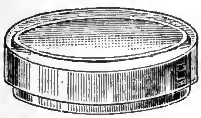


Fig. 434.—Dish Devised by Petri.
Used almost exclusively for plating; the most convenient diameter is from 100 to 120 mm.

Esmarch's Tube Plates.—Three or more tubes of sterile agar or gelatin, each tube not containing more than two or three cubic centimeters of the medium, are liquefied and inoculated as directed for the Petri dish method. A channel is made on the upper nearly flat surface of a block of ice by laying upon it a test-tube of the same size as those to be used, filled with hot water and corked, the stoppered end projecting beyond the edge of the ice; this tube is rolled over and over in the same spot until the channel half buries it, the bottom being a little lower than the corked end. Into this groove one of the infected tubes is laid so that the medium flows up to within two centimeters of, but *does not touch*, the cotton; the tube is then rolled, at first slowly, then more quickly,

until, within the first minute, it is spun rapidly; the medium in this way is congealed over the entire inside of the tube nearly up to the cotton; if the latter comes in contact with the medium, it prevents easy removal of the plug by making it stick to the side of the tube. Each tube is treated in the same way, after which it is labeled as directed for other plates. When set, the tubes are placed on end. With gelatin this can be done quickly; with agar, however, the tube must be kept in a nearly horizontal position for several hours, generally overnight, otherwise the agar may slip down.

After the plates are made by either of the foregoing methods growth of the bacteria is awaited; agar may be incubated. At the end of a varying period the colonies appear as distinct dots in and on the culture medium. In plate *a* they are commonly too close together to be distinct; plates *b* and *c* will be better. Select an isolated colony and transplant into a test-tube in the following manner:

Heat to redness the entire length of the platinum needle, at the same time exposing to the flame all of the glass rod that is likely to enter the test-tube, bottle, or dish. If the colony to be removed is within a bottle or test-tube, it is best to bend the tip of the inoculating wire like the

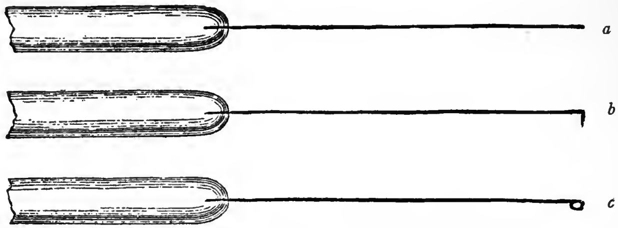


FIG. 435.—PLATINUM INOCULATING NEEDLES MOUNTED IN GLASS RODS.
Showing the shape of the ends as may be found useful for: *a*, stab cultures and stroke cultures; *b* and *c*, stroke cultures and smear cultures.

letter L; immediately after sterilizing the needle, holding it like a pen in the right hand, take the bottle and test-tube or both test-tubes in the left hand; remove the plugs from the tubes or bottles by grasping the projecting cotton of both tubes between the middle finger and ring-finger and the ring-finger and little finger of the right hand; pass the lip of the bottle or tube through the flame to burn off any adhering dust; introduce the needle into the bottle or tube, and lightly touch the colony from which it is desired to obtain a culture; this will infect the needle; quickly withdraw the needle and pass it into the tube containing the medium to be inoculated. The inoculation made may be: (*a*) a **streak** or **stroke culture,** in which case the needle is drawn from below upward in a straight line over the slanting surface of an agar or blood-serum tube; (*b*) a **smear culture,** made by gently rubbing the infected wire over the surface of the medium; or (*c*) a **stab culture,** made by a straight needle-thrust, from above downward, through the medium. Stroke and smear cultures are the most used on all solid media except gelatin, in which stab cultures are best. In transplanting from a Petri dish culture, the lid is raised barely enough to introduce the previously sterilized needle, which is then touched upon the colony, removed, and applied to the culture tube as previously directed.

The platinum needle used in bacteriologic work consists of a platinum wire, from one millimeter to two millimeters in thickness and from five centimeters to eight centimeters in length, fused into the end of a glass rod about five millimeters in thickness and from fourteen centimeters to eighteen centimeters long. The rod is used as a holder or handle for

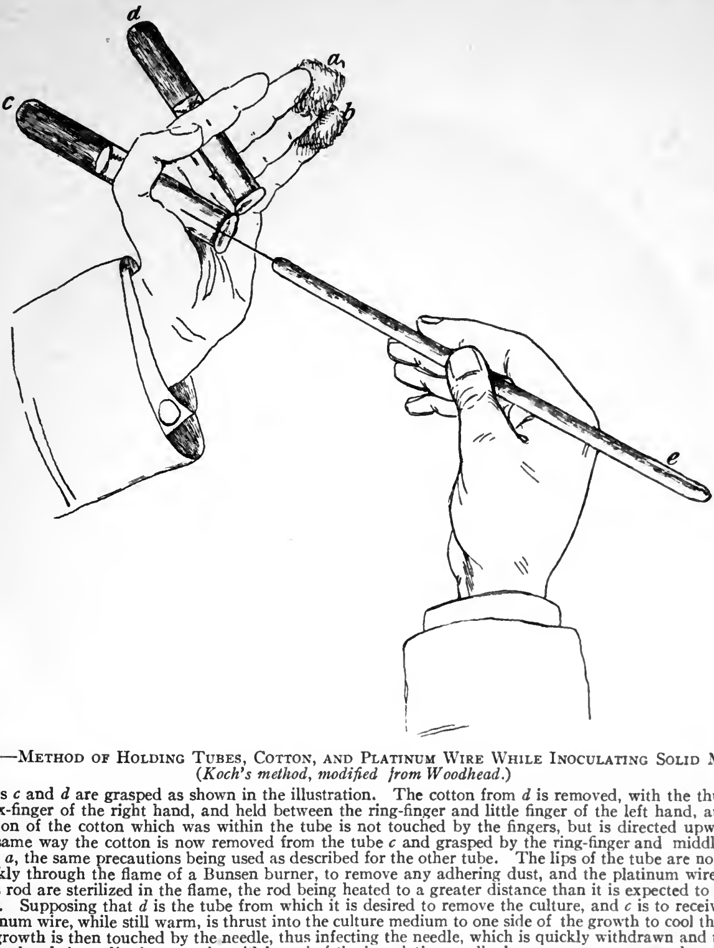


Fig. 436.—Method of Holding Tubes, Cotton, and Platinum Wire While Inoculating Solid Media.—(*Koch's method, modified from Woodhead.*)

The tubes *c* and *d* are grasped as shown in the illustration. The cotton from *d* is removed, with the thumb and index-finger of the right hand, and held between the ring-finger and little finger of the left hand, at *b*; that portion of the cotton which was within the tube is not touched by the fingers, but is directed upward. In the same way the cotton is now removed from the tube *c* and grasped by the ring-finger and middle finger as at *a*, the same precautions being used as described for the other tube. The lips of the tube are now passed quickly through the flame of a Bunsen burner, to remove any adhering dust, and the platinum wire and the glass rod are sterilized in the flame, the rod being heated to a greater distance than it is expected to enter the tube. Supposing that *d* is the tube from which it is desired to remove the culture, and *c* is to receive it: the platinum wire, while still warm, is thrust into the culture medium to one side of the growth to cool the needle; the growth is then touched by the needle, thus infecting the needle, which is quickly withdrawn and the tube *c* inoculated; *immediately upon the withdrawal of the inoculating needle* the cotton stoppers are placed in their respective tubes, and the *needle is at once sterilized* and set aside. *Never lay down an infected needle.* The tube inoculated is labeled, dated, etc., and set aside for observation. All this can be done quickly, and the beginner should practice the manipulation on tubes of media which are not infected; if they become infected during the process, his technic is faulty, and should be perfected before working with pure cultures.

the loop. The latter is variously curved, looped, or may be used straight, as for stab cultures. (See Fig. 436.)

Bacteriologic Examination of Water and Other Fluids.[1]—Sterilize a

[1] Bacteriologic examinations of water and air are introduced here as good examples of the practical application of improved plating methods, and in order that the student may familiarize himself with the technic of preparing plates and securing pure growths therefrom.

container in the hot-air sterilizer, and collect the water for examination. As bacteria multiply very rapidly, the examination should be made as soon as possible after collection; after a few hours' stand, particularly if the weather be warm, the results obtained will be without value as to quantity of bacteria.

Prepare a dozen Petri dishes and a corresponding number of tubes for plating. Sterilize two burets so graduated as accurately to measure

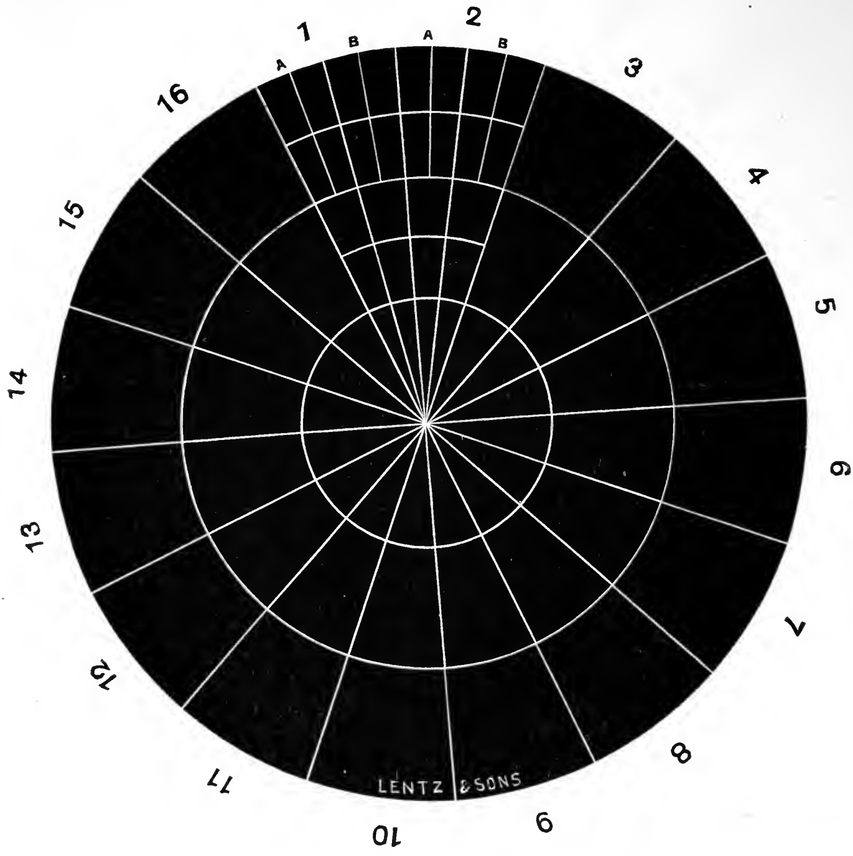


Fig. 437.—Apparatus for Counting Colonies.—(*Pakes.*)
Petri dishes are placed upon the ruled circle, and the colonies counted as drected in the text. An ordinary slate may be ruled as in the above figure and used for the same purpose.

0.02 to 1 c.c. Thoroughly agitate the water in order to diffuse the bacteria equally throughout the specimen, and fill a sterile buret with the sample under examination. The test-tubes of media, gelatin, or agar having been fully liquefied, are cooled to 45° C. in a water-bath; to each of two of the tubes is added 0.02 c.c. of the infected water; to another pair of tubes 0.05 c.c. of water is added; to another, 0.075 c.c.; to another, 0.1 c.c.; to another, 0.5 c.c.; and to another, 1.0 c.c. The tubes are thoroughly shaken, immediately poured in the usual way, and

set aside for the colonies to develop. If agar has been used, the plates may be incubated. As soon as the colonies develop they are counted. A Petri dish counting apparatus may be used, or a slate upon which has been ruled a diagram like that shown in figure 437. All the colonies in the plate may be counted or the number determined in one, two, or more of the wedge-shaped areas bounded by the radii and the arc, and the resulting number found for one wedge-shaped area multiplied by the total number of divisions—sixteen. The number of colonies found in the whole plate represents the number of bacteria in the water used for the plate. For example: Several areas counted give an average of twenty colonies to each area; there are sixteen areas: $20 \times 16 = 320$, the total number of colonies in the plate; assuming that the quantity of water used in making the plate was 0.1 c.c., then one cubic centimeter contains ten times 320 or 3200 bacteria. If different quantities of water are used, the result, reduced to the unit,—say, one cubic centimeter,—should be approximately the same, one series being a control for the others.

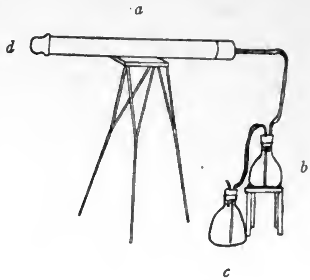


Fig. 438.—Hesse's Aeroscope.

This consists of a hollow cylinder of glass, *a*, sixty centimeters in length, four centimeters in diameter, plugged with cotton at both ends, sterilized, and charged with a layer of culture, much as the Esmarch plates. The two ends are covered by caoutchouc, one of the rubber caps having a hole to admit a glass tube by which the tube *a* is connected with the gravity flask *b*, which is further connected to the flask *c*. The flask *b* is filled with water. When ready for use, the rubber cap and the cotton plug at *d* are removed, the flask *b* is tilted so that the contained water flows into the flask *c*, thereby aspirating as much air into the tube *a* as water is allowed to flow from the upper to the lower flask. The tube *a* is now plugged and set aside for colonies to develop. These can be counted and transplanted as in other plate methods. Petri has improved the foregoing by substituting for the tube *a* a short tube packed with sand and sterilized, aspirating air through it, and then mixing the sand with gelatin and pouring into plates. Sedgwick and Tucker use sterilized granulated sugar instead of the sand. The sugar and sand methods give the best results.

In the examination of sewage and of other materials exceedingly rich in bacteria the large number of organisms present in even the smallest, most easily measured quantity may be too great for satisfactory counting. To avoid this difficulty the material to be examined is diluted with an equal quantity of sterile water; should this not be sufficient, further dilutions may be made. In the final calculation the dilution must be taken into consideration.

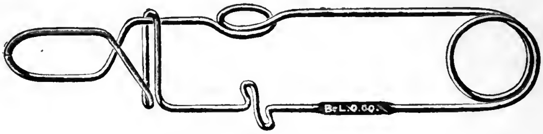
The foregoing test determines the number of bacteria in the sample. If it is desired to find what germs are present in the water, to make the test complete, the colonies are transplanted and studied as already directed when considering pure cultures. (See table illustrating the method of recording principal characteristics of an organism, p. 932.)

Bacteriologic Examination of Air.—The principle upon which the examination is conducted is to depend either upon sedimentation upon a sterile surface, as a Petri dish containing media,—a very unsatisfactory method,—or to secure the bacteria in a sterile filter by aspirating through it a known volume of air. Fig. 438, with the attached legend, will explain the methods used.

Staining Bacteria.—Staining bacteria greatly facilitates the study of their morphologic characteristics. For this purpose the anilin dyes are almost exclusively used.

The anilin stains commonly used in the laboratory are fuchsin,

gentian-violet, methylene-blue, and a few others; they are all applied in practically the same manner. For stock, it is best to keep the dye as a saturated alcoholic solution. For staining, however, alcoholic solutions are of little value, as they do not seem to possess the penetration of watery solutions. The usual strength employed is a one to two per cent. aqueous solution of the dye; the stains are unpleasant to handle and may be prepared as follows: To a test-tube—diameter 13 mm. to 15 mm.—two-thirds full of distilled water add, drop by drop, a saturated alcoholic solution of the dye until the water is barely transparent. This is then poured into a bottle adapted with a Barnes dropper. (See cut of appropriate stain bottle, p. 46.) The solution so prepared is about 1.7 per cent., and may be used whenever a one or two per cent. solution of the dye is recommended. The addition of carbolic acid to aqueous solutions of some anilin dyes seems to enhance their staining power and keeping properties. For this reason, instead of plain distilled water, as previously recommended, many workers use a five per cent.



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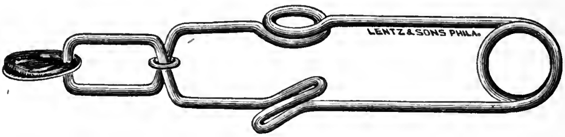


FIGS. 439 AND 440.—TWO FORMS OF STEWART'S COVER-GLASS FORCEPS.

Method of holding cover-glass and applying the stain. Convenient for blood work, and absolutely necessary for bacteriologic work; useful also in sputum examination, etc. The lower instrument shows a cover-glass with stain in position. If the cover-glass be grasped with the film or spread side toward the side of the forceps that has the circular bend intended to fit the thumb, shown at A, there will be no danger of losing trace of the side containing the spread, as this side of the forceps is practically always upward.

aqueous solution of chemically pure carbolic acid. It is of the greatest importance that the carbolic acid should be pure; many of the samples of the commercial acid contain impurities that are injurious to the anilin dyes.

One of the most useful stains is the *Koch-Ehrlich anilin water gentian-violet solution.* This should be freshly prepared as, at best, it keeps but a few days. Take, in a test-tube, about twenty cubic centimeters of distilled water; add anilin oil, drop by drop, shaking thoroughly until no more of the anilin is dissolved, the drops floating on and in the water, which may become milk-like as the result of emulsification of the oil; filter until clear: usually one filtration is enough, but occasionally two or three are required.

Formula for stain:

Saturated solution of anilin oil in distilled water,...	100 parts.
Saturated alcoholic solution of gentian-violet, methyl-violet, or fuchsin,.......................	11 "
Alcohol,.....................................	10 "

As it is not desired to stain laboratory utensils any more than can be avoided, it has been found that practically the same results as those secured by measuring can be obtained by dropping the solutions: 100 drops of the anilin water, 21 drops of the alcoholic solution of the dye, and 20 drops of alcohol.

Löffler's Alkaline Methylene-blue Solution:

Saturated alcoholic solution of methylene-blue, . . .	3 parts
Aqueous solution of caustic potash (1:10,000), ...	100 "

Ziehl's Carbolfuchsin.—For formula, see page 49. This is probably the most useful bacterial stain yet introduced.

To Stain Bacteria.—Thoroughly cleanse, dry, and polish a cover-glass; grasp it with cover-glass forceps and pass through the flame a number of times to burn off any adhering bacteria or other organic material; avoid over-heating, as the cover may warp or crack. Spread on this, with a previously well sterilized platinum loop or needle, a thin film of the material; permit it to dry *without using any artificial heat.* It is then "fixed" by passing through the flame, as follows: Stand about thirty centimeters from the flame and carry the cover-glass through a circle, the diameter of which is represented by the distance between the flame

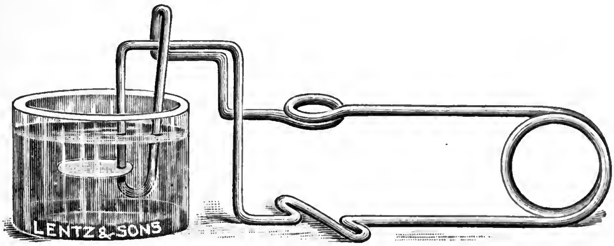


FIG. 441.—KALTEYER'S COVER-GLASS FORCEPS.

This instrument may be used exactly as the forceps shown in figures 439 and 440; in addition, it may be used as in the illustration. The danger of forgetting which side of the cover is coated is less than with any other type of forceps.

and the worker; pass it through the flame three times. Stain from two to ten minutes; wash thoroughly in water, dry, and mount with the film side downward. Films must be thoroughly dried before mounting; evaporation of the water accomplishes the same result as the application of alcohol in sections—dehydration; the use of a clearing agent, such as creasote or cedar oil, is usually unnecessary, as the residual oil present in the balsam will clear satisfactorily, provided the film is dry. The presence of either alcohol or water in the film when mounted on balsam leads to more or less emulsification of the residual oil in the balsam and consequent clouding.

Temporary mounts are often made, thereby avoiding the use of reagents so disagreeable and sticky as damar or balsam. If the examination is to be made with a dry lens, the film is turned over, with the spread side downward, upon a drop of water, the excess of which is removed to prevent the cover-glass from floating. When an oil-immersion lens is to be applied, the most satisfactory temporary mounts are made in immersion oil. The thoroughly dried film receives in its center a

droplet of cedar oil, and is then inverted on the slide; a droplet of oil is placed on its upper surface, and the examination is proceeded with in the usual manner. For method of focusing immersion objective, see page 51. Spreads can be made directly on the slide, followed by fixation, staining, etc. Such spreads may be examined without a cover-glass—a method commonly in vogue, but one with which the writer is not in sympathy.

Weigert's Method for Sections of Tissue Containing Bacteria.—Place sections for from six to eighteen hours in a one per cent. aqueous solution of any of the basic anilin dyes; after removal from the stain, wash in one-half saturated solution of potassium carbonate, then in distilled water, next in sixty per cent. alcohol, and finally dehydrate in absolute alcohol; clear in oil of cloves, xylol, or cedar oil, and mount in xylol balsam. Heating the stain or using a stronger solution hastens the process, but the results are less satisfactory. In case the particular basic dye used gives an unsatisfactory result another should be tried, using the same formula and method.

Gram's Method may be used either for cover-glass films, prepared in the usual way, or for sections. Stain in the Koch-Ehrlich solution made with gentian-violet (see p. 912), from two to five minutes, rarely twelve or twenty-four hours; rinse for a moment in water, and apply Gram's solution.

Gram's Iodin-iodo-potassic Solution:

Iodin,	1 part.
Potassium iodid,	2 parts.
Distilled water,	300 "

In films, after one or two minutes, the iodin solution is washed off with water, followed by alcohol. From time to time the cover may be mounted in water and examined with a $\frac{1}{6}$-inch or $\frac{1}{8}$-inch objective, and as soon as the excess of dye and precipitate has been fully removed, it may be dried and mounted in xylol balsam.

As soon as the section becomes dark brown, wash in sixty per cent. alcohol, dehydrate in absolute alcohol, continuing the latter as long as any perceptible amount of color is discharged, clear in oil of cloves or cedar oil in which a small amount of color may be discharged, pass through one or two changes of xylol, and mount in xylol balsam. After washing in sixty per cent. alcohol, sections may be contrast stained with carmin or hematoxylin, or with a one per cent. aqueous solution of vesuvin or Bismarck brown.

Neisser's method of **spore staining** consists in preparing the film in the usual manner, floating it upon the Koch-Ehrlich solution (made with gentian-violet) in a watch-glass, and heating to near the boiling-point for an hour. The film is next washed in water and decolorized by a solution composed of twenty-five parts of hydrochloric acid and seventy-five parts alcohol. This removes the stain from the bacilli, but if not allowed to act too long, leaves the spores stained. The preparation is next stained with methylene-blue, washed in water, dried, and mounted.

Flagella Staining.[1]—Löffler's method requires two fluids, the first

[1] See also Johnston and Mack, "Amer. Med.," May 7, 1904.

being a mordant, the second the stain. First solution consists of:

Aqueous solution of tannin (20 gm. tannin to 80 c.c. water),	10 c.c.
Aqueous solution of ferrous sulphate, saturated in the cold,	5 c.c.
Saturated alcoholic solution of fuchsin,	1 c.c.

The coloring solution is composed of saturated solution of fuchsin in anilin water, to which are added a few drops of caustic soda (1 : 1000) until opalescence commences. The mordant is applied to the cover-glass film, heating slowly over the flame for one minute.. It is not necessary for the liquid to boil. Wash in distilled water and then in alcohol. Stain by placing on the film a drop of the alkaline staining solution, heating again gently for one minute; wash in distilled water, dry in air, and mount.

Different species of bacteria require an acid or alkaline reaction to the mordant, and for this purpose two solutions are necessary: (1) Caustic soda, one per cent. aqueous; (2) an aqueous dilution of sulphuric acid, of which one cubic centimeter just neutralizes one cubic centimeter of the alkaline solution. For spirillum of cholera, one-half to one drop of the acid solution to sixteen cubic centimeters of the mordant; for Bacillus typhosus, two cubic centimeters of the alkali to sixteen cubic centimeters of the mordant, and so on; the number of drops of either solution can be determined only by experiment upon the organism in question. The Bacillus pyocyaneus and many varieties of the spirillum require an acid reaction, while the Bacillus typhosus, Bacillus subtilis, bacillus of malignant edema, and bacillus of symptomatic anthrax require an alkaline reaction.

Pitfield devised the following stain for flagella, using but one solution for mordant and stain:

(A)	Saturated aqueous solution of alum,	10 c.c.
	Saturated alcoholic solution of gentian-violet,	1 c.c.
(B)	Tannic acid,	1 gm.
	Distilled water,	10 c.c.

These are made separately, filtered and mixed. The resulting mixture—stain and mordant combined—is applied and heated gently almost to boiling-point, washed in water, dried, and mounted.

McCrorie's flagella stain is a single fluid having the following composition:

Night blue, saturated alcoholic solution,	10 c.c.
Tannic acid, 10 per cent. aqueous solution,	10 c.c.
Alum, 10 per cent. aqueous solution,	10 c.c.

Spreads are made from cultures eighteen to twenty-four hours old; the film is dried and fixed as usual. The stain is applied for two minutes cold and then warmed until a faint haze of steam is given off. Wash thoroughly in water, dry, and mount in balsam. Of the many stains for flagella that have been advised, this seems to yield the best results.

Duckwall's Flagella Stain[1]: Using gentle heat dissolve 2 gm. of tan-

[1] "New York Med. Jour.," June 24, 1905, p. 1253.

nin in 15 c.c. of water; add (1) 5 c.c. of an aqueous solution of ferrous sulphate saturated in the cold, (2) 1 c.c. of a saturated alcoholic solution of basic fuchsin; and 0.5 c. c. to 1 c.c. of a one per cent. aqueous solution of sodium hydroxid; filter through two papers. The spreads are prepared by mixing a drop of water of condensation from a twenty-four hour old agar culture with a drop of sterile water on a perfectly clean cover-glass, which is then tilted from side to side, to distribute the bacteria; dry under a bell-jar. Flood the dried film with the above solution and heat over flame until vapor arises, continuing to heat for one or two minutes. Add a few drops of 95 per cent. alcohol, rock the cover, and rapidly flush with water. After washing drain the cover, touching its edge to bibulous paper, and apply stain consisting of fuchsin 1 gm., absolute alcohol 13 c.c., of a 5 per cent. aqueous solution of carbolic acid 100 c.c.; heat gently for one or two minutes and almost boil for thirty seconds; add a few drops of 95 per cent. alcohol, wash with water, and dry under a bell-jar. Both mordant and stain give better results when not over twenty-four hours old.

Buerger[1] recommends the following method for **staining capsules:** Sputum, pus, or other albuminous fluid containing the organism is spread on a perfectly clean cover-glass; as soon as the edges begin to dry, the film is covered by Zenker's solution (p. 35), omitting the acetic acid. Warm over the flame about three seconds, rapidly wash in water followed by alcohol, tincture of iodin, and finally thoroughly wash with alcohol and dry in the air. It is then stained in a mixture consisting of anilin oil 10 c.c., water 100 c.c., thoroughly mixed and filtered, and 5 c.c. of a saturated alcoholic solution of gentian-violet. The stain should act for from two to five seconds, after which time it is washed off with a two per cent. aqueous solution of salt, in which it is mounted, and ringed with vaselin. The success of the stain demands the presence of a proteid, usually supplied by exudates, but when stains are to be made from cultures it must be artificially added. A drop of blood-serum diluted with an equal quantity of salt solution, or ascitic or pleural fluid, is placed on a cover; the bacteria to be stained are mixed with this diluted serum and spread evenly over the surface; from this point the technic is the same as that given for sputum and pus.

Hiss[2] recommends staining in a concentrated solution of gentian-violet heated until steam arises; wash in twenty per cent. aqueous solution of copper sulphate; blot on filter, dry and mount in balsam.

Microscopic Examination of Stained and Unstained Mounts.—In tissues stained by any of the methods given, the location, under a low power,—$\frac{1}{6}$-inch objective,—of bacteria can often be inferred by agminated areas of the dye known to stain such organisms. Having located such an area, a higher power may be used. Always begin the examination with a low power.

(For description of microscope and method of using same, see pp. 51 to 52.)

Gas formation may be investigated in connection with a study of yeasts. Thus, if a saccharometer charged with a sterile culture fluid containing glucose be inoculated with the Saccharomyces cerevisiæ, gas collects in the measuring-tube, showing its production by the growth

[1] "Medical News," December 10, 1904.
[2] "Jour. of Experimental Medicine," vol. vi, p. 335.

of the yeast. In addition to the evolved gas, it can be shown that the fluid contains other substances; simultaneously with the gas production alcohol is elaborated. The equation is written as follows:

$$\text{Glucose } (C_6H_{12}O_6) = \text{Alcohol } (2C_2H_6O) + \text{Carbon Dioxid } (2CO_2).$$

The study of gas formation is conducted for other organisms after the same method as described for the yeasts; while saccharine fluids are mostly used for this study, other media have also been found available.

Gelatin or agar *shake cultures* are sometimes used to detect gas formation.

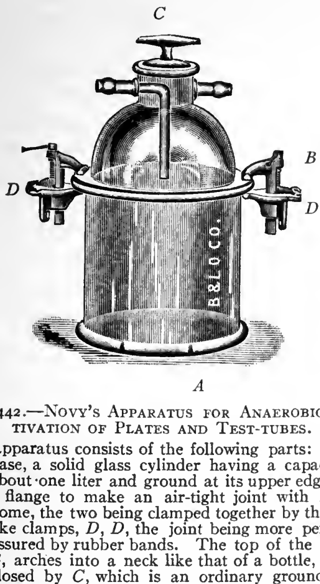


FIG. 442.—NOVY'S APPARATUS FOR ANAEROBIC CULTIVATION OF PLATES AND TEST-TUBES.

The apparatus consists of the following parts: *A*, the base, a solid glass cylinder having a capacity of about one liter and ground at its upper edge with a flange to make an air-tight joint with *B*, the dome, the two being clamped together by the vise-like clamps, *D*, *D*, the joint being more perfectly assured by rubber bands. The top of the dome, *B*, arches into a neck like that of a bottle, and is closed by *C*, which is an ordinary ground-glass stopper ground into the mouth of the neck, to the dome *B*. Through the side of the glass stopper, *C*, are two openings, so arranged that when *C* is turned as shown in the cut the openings permit gas to pass into the interior of the apparatus through either of the tubulatures shown at the side of the neck. On the inside of the stopper an L-shaped tube is fused, so that any gas carried into the apparatus through that tubulature passes below the level of the opposite tubulature.

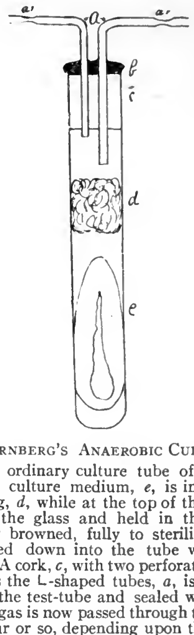


FIG. 443.—STERNBERG'S ANAEROBIC CULTURE TUBE.

The tube is an ordinary culture tube of rather large size. The culture medium, *e*, is inoculated, the cotton plug, *d*, while at the top of the tube, is cut even with the glass and held in the flame until thoroughly browned, fully to sterilize it, and is then pushed down into the tube with a sterile glass rod. A cork, *c*, with two perforations, through which pass the L-shaped tubes, *a*, is fitted to the mouth of the test-tube and sealed with wax at *b*. Hydrogen gas is now passed through the apparatus for an hour or so, depending upon the size of the tube, until all the air is displaced; the entrance and exit tubes are then sealed at *a' a'* by fusing the glass. The advantage of this simple method is that any tube can be used with any of the common media in use in the laboratory.

Either medium is liquefied, cooled to below 50° C., and inoculated while liquid; it is then thoroughly agitated and allowed to solidify. The growth of organisms producing gas will be evident by the appearance of small bubbles throughout the medium. The test is, at times facilitated by using a medium containing glucose, in which case the reaction may be identical with that previously described; in many cases it is, however, a much more complex problem.

Anaerobic Cultures.—*Novy's Apparatus* (Fig. 442).—Petri plates, Esmarch plates, or culture tubes are placed inside; the dome, *B*, is put in position and secured by the vise-like clamps, *D*, *D*; the glass stopper

is turned as shown in the cut. The tubulature not having the L-shaped extension downward is connected with the hydrogen generator, and a constant stream of gas is carried through the apparatus for some hours. As soon as the air is displaced, the stopper, *C*, is rotated one-fourth of a turn, thus closing the connection between the tubulatures on the side of the neck and the inside of the apparatus. If carbon dioxid is used instead of hydrogen, it is admitted through the tubulature that communicates with the inside through the L-shaped piece. The author has fancied that the exclusion of air, when using hydrogen, was facilitated by attaching to the L-shaped piece a soft-rubber tube extending to the bottom of the apparatus; as air is much heavier than hydrogen, this device causes the gas admitted through the opposite tubulature to displace the air more rapidly. The method devised by Sternberg is explained in the legend beneath figure 443. A more recent appliance for excluding the air without the use of hydrogen or carbon dioxid is that devised by Wright. Its form and method of application are indicated in figure 444. Hamilton cultivates anaerobes in glucose-peptone-bouillon upon the surface of which he maintains a layer of olive oil 1.5 cm. deep; inoculations and removals are made with a sterile pipet thrust through the oil. The advantages of this method are its simplicity and the fact that prepared sterile media, always ready for anaerobic inoculation, can constantly be kept on hand.[1]

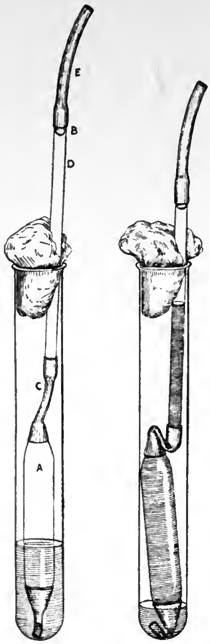


FIG. 444.—WRIGHT'S METHOD FOR ANAEROBIC CULTIVATION IN LIQUID MEDIA.

A. Spindle-shaped glass tube, at the lower end of which is attached a short piece of rubber tubing (lower B). C. Rubber tubing connecting upper end of A with lower end of D. D. Glass tube stoppered with cotton at upper B, and continued upward by the rubber tube E. For use, the apparatus is prepared as shown on the left, sterilized by steam, and may be kept in stock. Before inoculation the medium in the tube is boiled to drive off absorbed gas, cooled, and inoculated. Suction is applied to the rubber tube E, drawng the contained fluid upward to point indicated in drawing on the right; the tube is then thrust downward, kinking the rubber tube C, and in a similar manner closing the rubber tube at the lower end of A. It is claimed that this apparatus affords a ready method of securing, at the same time, both aerobic and anaerobic cultures in the one tube.

Hanging-drop Cultures for the Demonstration of Motility.—If a drop of liquid culture be placed on a slide and covered in the usual manner, examination with a high power will usually demonstrate the motility of an organism. This crude method is not accurate, as heat currents always occur in fluids under a cover-glass, and may mislead the observer. For demonstrating motility the drop-culture slide is used. This consists of a thick slide of the same dimensions as the ordinary microscope slide, with a concavity ground in its center. A clean cover-glass is grasped in the forceps and is passed through the gas-flame to sterilize it. The concave slide is prepared in the same way, allowed to cool, and around the concavity is painted a thin line of any nonvolatile oil—

[1] For full review of newer anaerobic methods see Stuler, "Centralbl. f. Bakt.," Oct. 17, 1904, p. 298; also "Jour. of Applied Microscopy," March, April, and May, 1902.

ordinary sperm oil, vaselin, or, when the slide is to be incubated, paraffin or oleum theobroma liquefied by gentle heat. A droplet of the culture in bouillon or Dunham's solution is placed in the center of the cover-glass, which is then inverted over the hollow slide, care being taken that the droplet is very small,—not larger than a small pinhead, so that it will not sway from side to side,—and that it does not come in contact with the slide at any point. With the stage of the microscope perfectly horizontal, the droplet is carefully focused. The moving bacteria can be easily seen, provided the illumination is satisfactory; the iris diaphragm should be closed to admit but little light, otherwise the field will be so flooded with light that the small, colorless bodies—the bacteria—may escape detection. It is often advisable to center the drop with a low power—say, a $\frac{1}{2}$-inch or $\frac{2}{3}$-inch objective—before attempting to focus with a high power. If the organism is growing on a solid medium, a small part of the culture is mixed with the bouillon or Dunham's solution on a sterile cover, and the hanging drop prepared from the mixture.

The "hanging-drop culture"—as such the foregoing is known—may be incubated and kept under observation for a long time if care is used to avoid infection during its preparation and to exclude bacteria by a perfect oil seal. By incubating hanging drops, bacteria can be seen dividing, yeasts watched while forming and throwing off buds, and other observations made. (See Widal's test, p. 929.)

Fig. 445.—Drop-culture Slide.
(75 × 25 mm., of polished plate glass, with a cavity 18 mm. in diameter.)

During the growth of many bacteria, bodies are elaborated that change the **reaction of the culture medium.** This test is applied by adding an indicator to the fluid, or other medium, and observing whether the color of the indicator changes. The two indicators most commonly used are litmus and phenolphthalein; the former is kept in stock as a tincture, and the latter as a 0.1 per cent. solution of the salt in fifty per cent. alcohol. To apply the test, a number of tubes of culture media—milk, bouillon, or, what is best of all, Dunham's solution—are prepared; although much less suitable, solid culture media, such as gelatin, agar, or potato, may be used. In bulk, some of the medium—sufficient to fill several test-tubes of the size intended for use—has added to it enough of the indicator to show, faintly but clearly, the reaction; one part of the medium should be but faintly acid, very dilute acetic acid being used to acidify; another portion should be rendered faintly alkaline by the use of one per cent. caustic potash, while a third is neutral. With great care sterile media may be sensitized without subsequent sterilization; as a rule, however, after sensitizing it is necessary to re-sterilize. The same quantity should be in each tube. A number of tubes belonging to each series are inoculated with the germ in question, and several are left as test or control reserves. In the course of a few days, often in less than twenty-four hours, it will be observed that the reaction of the two series is changing. If the germ produces an alkaline reaction, the neutral series evinces the change first, followed by the acid

series becoming less markedly acid and, in some instances, eventually manifesting a clearly defined alkaline reaction. The alkaline series may show a slight intensification of the alkaline reaction or may not change at all. If the organism produces an acid, the reaction just given will be reversed. In either case the control tubes remain unchanged.

Rosolic acid is also used as an indicator; the stock solution is prepared by adding 0.5 gm. of the acid to 100 c.c. of eighty per cent. alcohol. Its use is the same as the foregoing; it pales when acid, intensifies its rose-color when alkaline.

Indol.—Among the chemic tests applied for the identification of bacteria is that for indol. Several tubes are charged with seven cubic centimeters of Dunham's solution, sterilized, and three or four inoculated with the germ under investigation, and twice the number reserved for controls. After twenty-four hours add to one of the controls ten drops of chemically pure sulphuric acid, and to another one cubic centimeter of a sodium nitrite solution, freshly prepared by dissolving one gram of chemically pure sodium nitrite in 10,000 c.c. of ammonia-free water. To the second tube also add ten drops of sulphuric acid. Both tubes should be watched for fifteen or twenty minutes; no color should develop, as they contained no indol. To one of the inoculated tubes add the sulphuric acid, and if in from ten to twenty minutes no reaction occurs, add the sodium nitrite solution, as previously directed; if indol be present, a distinct rose-color appears. Occasionally the rose-color may appear without the addition of the sodium nitrite, in which case the organism has produced not only indol, but also a reducing agent, commonly a salt of nitrous acid.

Thermic Disinfection.—Each organism thrives best at a certain temperature, known as its *optimum temperature*. Variations above or below the most favorable degree of heat influence the growth of the germ in question. The lowest temperature at which growth takes place is called the *minimum temperature;* the highest, the *maximum temperature*. The three thermal points are rarely the same for any two organisms, and hence constitute important tests in the identification of a germ under investigation. The *thermal death-point* is that degree of heat destroying the life of a germ; a knowledge of the point at which the organism is destroyed also aids in the differentiation of bacteria. The thermal death-point is not constant for the same microbe under all conditions, varying, in some cases, with the age of the organism, the presence or absence of moisture, etc. Again, moist heat is usually destructive to bacteria at a lower temperature than dry heat; and moist heat under pressure (superheated steam) more penetrating and more rapidly fatal than dry heat at the same temperature.

In order to determine the thermal death-point of a given organism all the foregoing factors must be borne in mind, as well as the length of time of exposure. The latter also varies with the conditions under which the test is made. A temperature of 70° C., moist or dry, and continued for one or two hours, may be, to a given organism, as certainly fatal as 100° C. with an exposure of ten minutes. The thermal death-point in the presence of moist heat is commonly determined by exposure of bouillon cultures, infected material, or dried threads—prepared as described under Chemic Disinfection (see below)—to different temperatures and for different lengths of time in the steam sterilizer (Fig.

431, p. 905) or in the autoclave (Fig. 432, p. 906). In making the test with dry heat the hot-air sterilizer (Fig. 428, p. 903) is used, and previously dried infected materials, especially dried threads, make the best test-objects. After exposing the infected material to heat, inoculations are made upon suitable culture media; the tubes are incubated and kept under observation a sufficient time for the development of any undestroyed germs. The thermal death-point of an organism may be determined even before its successful cultivation. Such an experiment is permissible only when we can not successfully cultivate the germ. In order to make the test we must be able to infect an animal. Material that is known to contain the organism in question is subjected to heat, and after definite exposures, is inoculated into susceptible animals. If disinfection has been complete, the inoculated animals escape. A source of error lies in the well-known fact that the pathogenicity of an organism may be lowered without of necessity destroying its viability; if, however, the experiment has rendered the germ no longer capable of inducing disease, its infectivity is removed, and therefore disinfection, in the theoretic sense, has been secured.

For determining the thermal death-point a number of factors must be considered, otherwise results can not be uniform. The following general plan is recommended by Dalton and Eyre:[1] Length of exposure, ten minutes; the emulsion used for the test to consist of 3 c.c. of sterilized normal salt solution or water to which has been added 3 mgm. of the culture from an optimum cultivation, the mixture exposed in a test-tube 1.5 cm. in diameter with wall 1 mm. thick. The exposure should be made in a thermoregulated water-bath. The thermal death-point to be the lowest temperature that will kill all the organisms exposed to it in the time limit of ten minutes.

Theoretically, there should be two death-points—a maximum and a minimum; but experience has satisfactorily proved that there is at present available no temperature sufficiently low to act as a disinfectant upon which it is possible to rely. Reduction below zero commonly determines only a stage of inactivity that ends with return of the organism to conditions again compatible with growth.

Chemic Disinfection.—In addition to the influence of thermic changes on bacteria, it is necessary to study the effect of disinfectants belonging to the chemic group. The relation of other physical agents than heat may also be studied: *e. g.*, drying, light, and electricity. In studying disinfectants, solutions are to be used almost exclusively; insoluble disinfectants are of more than doubtful value. Again, a culture medium must be used that does not alter the chemical in question. Thus, if, in the study of corrosive sublimate, a culture medium rich in albumin or strongly alkaline be used, the mercurial is instantly decomposed when it comes in contact with the culture medium, and, it may be, before it has had time to act upon the bacteria. Having found the desired culture medium, the next point to determine is the exact point at which the body under investigation ceases to be antiseptic: that is, inhibits the growth without of necessity destroying the life of the bacteria. For this purpose a series of tubes of culture media are prepared containing the antiseptic in varying quantities. These are best prepared, if possible, by taking 50 or 100 tubes of the medium it is desired

[1] "Jour. of Hygiene." April, 1904. p. 158.

to use, sterilized in the usual way: To ten of these enough of the agent is added to make the strength ten per cent.; to another ten, enough to make the strength five per cent.; to another ten, four per cent.; and so on, covering various percentages.

All these tubes are inoculated with the germ that it is proposed to use for the test. A series will be found in which dilution is so great that the agent no longer perceptibly influences growth of the germ; another series contains a sufficient amount of the germicide to inhibit reproduction but not destroy vitality; in the third group of tubes the microbe is killed. The strength at which disinfection—that is, destruction of reproductive power—occurs may be approximately inferred by diluting with the same sterile culture medium the tubes in which no growth has evinced itself, so that the proportion of the disinfectant in the dilution shall be less than that already found not to inhibit growth. After this dilution the bacteria that have not been destroyed develop, showing in what strength disinfection has been complete. This has, however, taken so much time—probably days—that doubt may still exist as to the rapidity with which the agent in question acts; and as the time required by a given solution to destroy viability is important, the rapidity of action and the necessary strength for practical disinfection must be determined. For this purpose a number of methods have been suggested, all of which are open to certain sources of error.

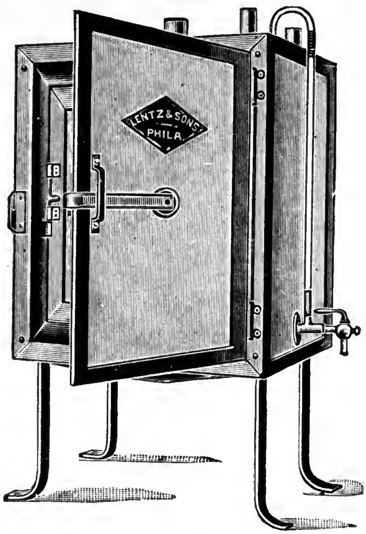


Fig. 446.—Small Incubator Sufficiently Large for Individual Work.

To a number of cultures in a liquid medium the agent in question is added, so as to make the percentage such as has been found in the previous test to be destructive; the added solution is thoroughly mixed with the culture, from which inoculations are made at intervals of minutes for as long as an hour. The removal must be made into tubes containing sufficient of the medium to dilute the material carried over beyond the strength already shown to have an inhibitory action, so that any undestroyed bacteria may be free to develop.

The source of error by this method lies in the clumping of the germs in the original tube; if grouped in clumps, the agent may not have penetrated the clumps. Penetration is a most important point, for without this power a disinfectant is of little practical value; as, in all purposes for which germicides are used, a certain degree of penetration is necessary, this apparent objection is not without its good side. To get rid of the clumps, cultures are made in a medium containing fine quartz sand; this is shaken up in the culture and the culture filtered through glass wool and the filtrate used for the test. Tubes containing the sand may have mixed with them growing cultures containing no sand.

Again, threads of silk from two centimeters to six centimeters in length may be placed in tubes of liquid culture media, the tubes sterilized as usual, and, when sterile, infected with the germ that it is intended to use for the test. When the culture is well grown, it is shaken, the threads are withdrawn, and may be used as test bodies to disinfect; they may be first dried in sterile dishes or they may be used moist. A source of error lies in the quantity of the disinfectant that the thread may convey into the tube into which it is transplanted after treatment with the disinfectant. In some cases this may be partly avoided by washing the thread in sterile water or in some solution, or by exposing it to a vapor, which, by chemic action, converts the disinfectant into an insoluble or inactive compound. Thus, threads which have been in corrosive sublimate solutions may be exposed to ammonium sulphid vapor, the solution converting the mercurial into an insoluble and inactive sulphid.

It will be noted that one of the essential elements is to make the transplantation, after treating the thread or culture with the disinfectant, into such a quantity of new noninfected medium as to insure a dilution beyond the inhibiting point, which may be due to any of the antiseptic carried over on the thread or on the platinum loop. Thus, if a thread has been exposed to a solution of an agent,—say, in the strength of 1 : 100,—and the inhibiting action is present in a solution having a strength of 1 : 1000, it will be necessary to carry the thread into a medium having a minimum bulk, in order to be safe, of at least 100 times the quantity carried over on the thread, thereby assuring such dilution as not to preclude the disinfectant preventing growth of any undestroyed organism.

In testing gases, threads, cultures, and other infected materials are exposed to the gas—either pure or with a known dilution of air—in a closed chamber, such as a bell-jar.

In addition to the foregoing system of tests, so-called *practical tests* are made. A known quantity of pus, blood, sputum, or feces is mixed with a known quantity of the disinfectant, and inoculations made at intervals of from two to five minutes. Varying strengths of the disinfectant are used with exposure for different lengths of time; in this way purely laboratory experiments are controlled by what are considered practical methods.

Again, animals may be inoculated with cultures or threads that have been exposed to disinfectants. In the latter case it is to be remembered that in rare instances the pathogenicity may be reduced without the germ being destroyed.

To study the pathogenesis of an organism **inoculation of animals** is necessary. The animals most used are rabbits, guinea-pigs, rats, and mice. The absolute requisite to success is careful asepsis at every stage of the process, and during the postmortem if the animal dies. If the disease or a disease is produced, and it is desired to obtain cultures, they must be secured with the same strict attention to detail.

All instruments used in the various stages of inoculation, examination during life, or postmortem, should be sterilized by heat: preferably dry, although moist heat may be used. Chemic disinfection must be regarded with suspicion, although syringes may be sterilized in a five per cent. solution of carbolic acid allowed to act for one or, better, two hours,

during which time the solution should be kept warm. Pure formalin may be used on instruments. No matter what chemic body is used, it must be thoroughly removed by washing in sterile water before proceeding with the operation. The hands of the operator and of the assistants, and the table upon which the operation is to be conducted, should be washed with soap and water as hot as can be tolerated, followed by alcohol, ether, and finally corrosive sublimate solution (1 part of the salt dissolved in 1000 parts of normal salt solution), which should be allowed to act several minutes, followed by thorough washing in sterile water.

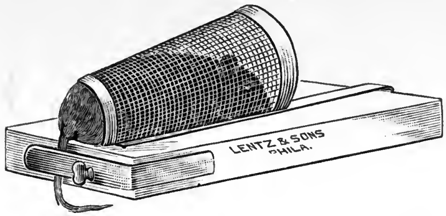


Fig. 447.—Apparatus for Holding a Mouse or Rat for Inoculation. (Devised by Dr. Lydia Rabinowitsch and Dr. Voges.)
The inoculation is usually made just over the root of the tail.

Of the many methods for inoculating an animal, the following will be found useful:

1. *Subcutaneous inoculation* is the one most frequently used. The site of the contemplated operation is shaved, washed with soap and water, water, alcohol, ether, alcohol, and corrosive sublimate solution (1 : 1000), and the last removed by thorough washing with sterile water. Between the scapulæ and near the tail are the most convenient sites for inoculation, but any point where the tissues are lax will answer the purpose.

The skin is stretched and made tense, an incision or pocket is made in the tissues about five millimeters to ten millimeters in length and correspondingly deep under the skin; into the pocket so made a loop of the growing organism or suspected material is introduced, after which a layer of sterile cotton is laid over the wound and a thick coating of collodion applied; in a few minutes this will dry; the animal is then liberated and kept with an uninoculated animal known as the control. Subcutaneous injection of bacteria, suspended in sterile water or bouillon, may be resorted to as directed for intraperitoneal inoculation.

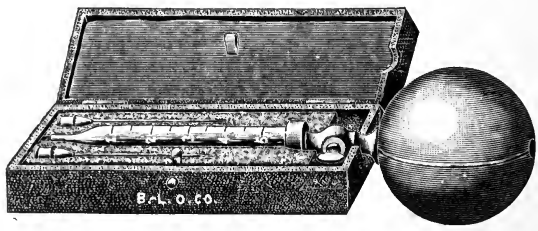


Fig. 448.—Koch's Syringe for Hypodermic, Intraperitoneal, and other Injection Methods for Inoculating Animals; the Capacity Should Be About Two Cubic Centimeters.

2. *Intraperitoneal injections* are made by preparing the animal as before. A syringe graduated in cubic centimeters is necessary for this method. The skin of the abdominal wall—the site of the operation—is prepared as previously directed, grasped by an attendant, and raised as a fold, into which the needle is introduced and forced onward into the peritoneum, then partly withdrawn to make sure it is free in the peritoneal cavity. The syringe is now attached, a given quantity of bouillon culture is introduced, and the wound is sealed. Rosenau[1] has greatly im-

[1] Hygienic Laboratory Bull. No. 19, 1904.

proved the Koch syringe, and describes a method for assuring accurate dosage.

3. Intravenous inoculation is made directly into a vein; the most convenient veins are those of the rabbit's ear. The overlying skin is prepared as already directed, and an incision is made down upon, but not into, the vein; when the vessel is thoroughly exposed, the needle of the hypodermic syringe is thrust into the vein in the line of the blood-current, and the contents of the syringe slowly injected. Great care must be used to see that no air enters the vein, and that no clumps or other solid material that might cause embolism are thrown into the blood.

4. Inoculation into the Anterior Chamber of the Eye.—Anesthetize the cornea by cocain, wash with sterile water, perforate the cornea at the scleral margin with a hypodermic needle, through which the material is injected; the quantity should be very small—scarcely a half drop; otherwise a disturbing tension is created that greatly modifies the result of the operation.

5. Tissue Implantation.—Sometimes (as in glanders and tuberculosis) a small piece of the suspected tissue is used for inoculating. The implantation may be made into the subcutaneous tissues or serous cavities. In the first instance a pocket is prepared as already directed for subcutaneous inoculation, into which the block of tissue (which should not be larger than from two to five millimeters cube—the smaller

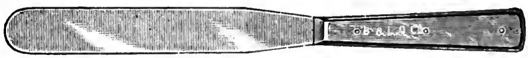


FIG. 449.—SPATULA USED FOR SEARING THE SURFACES OF ORGANS BEFORE MAKING INCISIONS INTO THEIR INTERIORS FOR OBTAINING CULTURE MATERIAL.

the better) is implanted, the wound sealed, if necessary, sutured, and covered as already directed. For transplantation into a serous cavity, the peritoneum is usually selected. Under the strictest asepsis the cavity is opened, the tissue dropped in, and the opening closed. In some instances, in order to assure vascularization, a tip of the omentum is brought out, the block of tissue rolled in the serous membrane, and the roll secured by a stitch. The foregoing methods demand the use of a piece of tissue of macroscopic proportions, and leave a wound through which accidental infection may occur. In many instances the difficulties just indicated may be evaded by rubbing up the material in a sterile glass mortar with a small quantity of sterilized water. Unless there is an unusual amount of connective tissue, the maceration may be sufficient to permit of injection through a medium-sized hypodermic needle. When there is reason to believe that the water may act deleteriously, some other menstruum, such as normal salt solution or blood-serum, may be used.

6. Inhalation.—By means of an atomizer bacteria suspended in water or other liquid medium are sprayed in such a manner that inhalation seems reasonably certain. So administered, necessarily many enter the alimentary canal and infection by that pathway may occur. For large animals (dogs, cattle, and horses) it is possible to introduce a tube past the epiglottis and in that way infect the trachea; usually tracheal infection is best accomplished by exposing the trachea in the

neck and injecting the bacteria directly into the tube. The lung may be infected through the chest wall by hypodermic injection.

7. Infection by the *reproductive* or *genito-urinary system* is rarely practised.

8. Feeding experiments are frequently employed. The bacteria from cultures or in the dried form are distributed on food, or infected tissues may be fed. When the gastric juice would probably destroy or render inert the particular germ, the stomach, before the experiment, may be washed out, or the gastric acidity neutralized by weak alkaline solutions. Less commonly the action of the stomach is evaded by a laparotomy and direct intestinal deposit of infectious material.

9. Infection of joint cavities, bones, muscles, etc., may be attempted in ways similar to those for subcutaneous and intra-abdominal inoculation.

10. Intracranial inoculation is performed in the following manner: Shave and antisepticize the scalp in the parietal region; with sterile hands and instruments raise a V-shaped flap of skin twice the size of the trephine to be used; with a trephine 0.5 cm. in diameter remove a button of bone, exposing the dura; if a mass of tissue is to be inserted, open the dura, introduce the tissue, and close the dura with a suture. Fluid or finely emulsified tissue may be injected with a syringe without incising the membrane. Suture the skin and seal with antiseptic dressing.

After-treatment of the Animal.—Medication of all kinds should be avoided; overcome the immediate shock by the gentlest handling of the animal, abundance of fresh air, and warmth. It should be treated exactly as a control (an uninoculated animal of the same species), but, as a rule, should be in a cage or inclosure by itself; otherwise the control may injure the inoculated animal.

The Postmortem.—If the animal dies, the body should at once be washed with soap and water and with water and alcohol, and immersed in 1 : 1000 corrosive sublimate solution, followed by washing with sterile water. A postmortem is made under strict asepsis. (See also p. 29.) As soon as the heart is exposed, a spot on the surface of the right auricle is seared by laying a heated spatula upon it; this thoroughly disinfects the surface. Thrust a sterile inoculating needle into the auricle, moving it through the blood backward and forward until a drop emerges along the side of the needle, when it is withdrawn and a tube of medium inoculated, which may be at once poured into a plate. (See Plate Methods.) This operation is repeated for each cavity of the heart and for all important organs of the body. Pieces of tissue are hardened, either in absolute alcohol or corrosive sublimate, and prepared for sections in the usual manner. (See Killing and Fixing of Tissues, p. 33; also Staining of Bacteria, p. 911.)

Preparation of Toxins and Antitoxins.—The preparation of the diphtheria and tetanus antitoxins is as follows: The bacilli are grown in flasks (1 L. to 2 L.) of bouillon, which in the case of tetanus must be arranged to assure anaerobiosis. For the satisfactory production of diphtheria toxin the bacilli should be grown in a thin stratum of an alkaline glucose-free bouillon; the maximum strength usually is attained during the second week. Filter through a Pasteur-Chamberland filter, preserve in well-stoppered bottles, and keep in a dark place. In doses

of 0.01 c.c. this filtrate should kill a guinea-pig weighing 500 grams in from forty-eight to sixty hours. For the purpose of immunizing animals, this fluid is in many cases too strong for the first injections, and should be diluted with one-fourth its volume of Gram's solution. Roux and Vaillard have determined that the toxin is much less dangerous when combined with iodin. For experimental studies small laboratory animals (rabbits) may be used, but for the production of antitoxin on a larger scale animals able to supply more serum are necessary; horses, cows, sheep, and goats are commonly selected. The weakened or modified toxin is administered hypodermatically at first, but after a relatively high degree of resistance has been attained it may be given intravenously. Toward the end of immunization bacteria themselves may be injected. The injection is repeated in a few days, and thus continued for several weeks. With each successive injection the proportion of Gram's solution should be diminished, and the dose slightly

FIG. 450.—STERNBERG'S FLASK, USED FOR COLLECTING FLUIDS, WATER, ETC., AND FOR HOLDING CULTURES IN LIQUID CULTURE MEDIA.

Before using, it is sterilized in the hot-air oven. To fill, the point is broken off and the bulb is heated, thus expelling some of the contained air; the point is then thrust into the fluid, and, as the bulb cools, the fluid rises into it; when the desired quantity is drawn into the bulb, the point is sealed in a gas-flame. Certain brands of antitoxin are now dispensed in bulbs similar to the one here illustrated.

FIG. 451.—KITASATO'S FILTER.

The material to be filtered is placed in the upper bulb which is connected with the central bougie of unglazed porcelain. The point of connection between the receiving chamber and the filter bougie is covered by a rubber cork, which fits very tightly into the neck of the flask. Through the lateral arm of the flask, extending out to the right, the air is exhausted from the interior. In this way filtration, ordinarily slow, may be accelerated by air pressure. The filter is mostly used for separating germs from their toxins.

increased until the pure toxin is reached. After injection of the toxin the animal not infrequently manifests a slight rise in temperature, with accelerated pulse, and sometimes an evident malaise. A second injection should not be given until all symptoms of the previous injection have disappeared. The amount of toxin is gradually increased until the animal bears without inconvenience a dose equal to 100 minimum fatal doses. If during this time a loss in body-weight becomes manifest, the injections should be discontinued; otherwise a fatal cachexia may develop.

The horse is easily immunized, and will supply large quantities of the antidiphtheric serum. Horses bear proportionately large doses better than other animals, and but a transient fever succeeds a dose of from two to five cubic centimeters of a strong toxin.

Antitoxin is obtained from the animal by bleeding under the strictest conditions of asepsis, receiving the blood through a cannula into a sterile jar, flask, or other container, as already directed for the preparation of blood-serum for culture purposes. The separated serum may be preserved by the addition of tricresol, thymol, carbolic acid, camphor, etc. It should be sterile, and if care has been taken to exclude contamination during the various stages in its preparation, the addition of a preservative is unnecessary. The milk of immune animals may offer an important source of the antitoxin.

In order to estimate the *strength of an antitoxin*, the minimum fatal dose of a toxin must first be known. This information is obtained by selecting a number of guinea-pigs, each of which weighs 250 gm., and by injecting subcutaneously different quantities of the toxin under investigation. The minimum fatal dose is that which kills a guinea-pig weighing 250 gm. inside of four days. In order to exclude possible error arising from unusual susceptibility or insusceptibility of the animal, a number of injections should be made and a fairly uniform result finally attained.

The strength of the antitoxin present in the serum, obtained as previously described, is expressed in *immunity units*. An immunity unit is the quantity of antitoxin which, when mixed with the toxin, neutralizes 100 minimum lethal doses of the latter. For the purpose of securing a uniform strength the U. S. Government now supplies a standard serum used by manufacturers for standardizing sera.

A number of test doses of the toxin are prepared, each containing a hundred times the minimum fatal dose. To each test dose is added a measured quantity of the serum in question. To one dose is added 0.01 c.c. of the serum; to another, 0.05 c.c. of the serum; to another, 0.1 c.c. of the serum; to another, 0.5 c.c.; and to still another, 1 c.c., and so on. The mixtures are now injected into guinea-pigs and the results observed. Animals not dying within four days were protected; local infiltration, wasting or death after the fourth day does not enter into the computation. The mixture containing the smallest amount of serum and yielding this result contains 1 immunity unit. If 0.05 c.c. of a serum neutralizes one hundred times the minimum lethal dose, each cubic centimeter contains twenty immunity units. Antitoxin, as placed upon the market, is labeled as containing a certain number of immunity units, and the measured quantity of serum necessarily varies, as the number of units obtained are rarely exactly the same in two animals. For the treatment of disease the antitoxin is administered subcutaneously.

In the production of antitoxins the tissues are immunized to toxic agents produced by the bacteria, while upon the germs themselves there is no direct action. If bacteria or other cells are injected the serum of the animal acquires the property of attacking the bacteria or other cells not only in the tissues but *in vitro* as well. The protection of the organism against the foreign substances is accomplished through the intervention of substances called bacteriolysins or cytolysins, and the process is called bacteriolysis in one case and cytolysis in the other. An important clinical application of this fact is in the diagnosis of typhoid fever. Theoretic considerations are discussed elsewhere (see

discussion on immunity), and at this point the technic only need be considered.

Widal's Test for the Diagnosis of Typhoid Fever.[1]—*Culture Employed.*—The culture used in the Widal test should be taken from an agar growth that has been allowed to develop at ordinary room-temperature for at least twenty days. From this agar culture inoculations are made into tubes containing neutral beef bouillon, and these tubes, after incubation at 37.5° C. for from eighteen to twenty-four hours, are used in the test. Instead of making bouillon growths, emulsions in sterile distilled water may be used with good results by thoroughly mixing a bit of a recent agar growth with about 2.5 c.c. of sterile water in a test-tube until a uniform cloudiness appears.

The precautions previously indicated must be followed to avoid certain false or pseudo-reactions, which sometimes occur when normal blood or blood from individuals suffering from diseases other than enteric fever, is added to a virulent culture of the typhoid bacillus.

Microscopic Method.—The blood is obtained by puncture of a finger, and three separate drops are allowed to fall upon the surface of a perfectly clean glass slide that has been passed through a flame and cooled just before use. The glasses are permitted to dry, and are then placed in a box to await examination at a convenient time.

To one of the blood-drops a large drop of sterile distilled water is added to effect a solution of the dried blood; and while this is going on, the other preparations for the test are being made, by cleaning and sterilizing by the flame two cover-glasses and a "concave slide," to be used for the microscopic examination of the specimen.

On one of the cover-glasses six drops of the typhoid bouillon are now placed, and to this is added a large drop taken with a platinum loop from the summit of the blood solution, and the whole is thoroughly mixed together. From this mixture of blood solution and typhoid bouillon a minute quantity is now placed with a platinum needle upon the center of the second cover-glass, which is immediately inverted over a hollow-cell slide, sealed with either vaselin or cedar oil, and examined under the microscope with a $\frac{1}{8}$-inch dry objective. (See Hanging-drop Culture, p. 918.)

Instead of the glass slide previously recommended for receiving the blood, a small piece of highly glazed paper may be substituted. Whether using the glass slide, cover-glass, foil, or paper, the blood as received at the laboratory is dry, and the difficulty that at once confronts the investigator is to restore this to its original volume. It does not seem probable that accurate restoration is ever possible, and for this reason the dry method must always be liable to error, depending upon our

[1] While largely used in laboratories for the diagnosis of typhoid fever the same principle may be applied to the diagnosis of paratyphoid, colon infections, paracolon infections, bacillary dysentery, Malta fever, and with less hopeful results to cholera, plague, tuberculosis, pneumonia, meningitis, anthrax, etc. The bibliography of serum diagnosis is most extensive. (See Craw, "Jour of Hygiene," January, 1905; Rostoski, "Manual of Serum Diagnosis," New York, 1904; Asakawa, "Zeit. f. Hyg. u. Infectionskrank.," xlv; Scheller, "Centralbl. f. Bakt.," Bd. xxxviii. p. 100; Ficker, "Berlin. klin. Woch.," 1903, No. 45; Borden, "Medical News," March 18, 1905, p. 485; Wood, "Chemical and Microscopical Diagnosis," 1905.) Full review of the subject by Rosenberger ("Amer. Med.," April 16, 1904, p. 621).

total inability accurately to determine the dilution used. The majority of observers favor a dilution of not less than one part of serum to forty parts of bacterial suspension, and for this purpose the writer is not familiar with any method that possesses advantages over that devised by Cabot.

A drop of blood is placed in a tube or other container, and at once, using the same pipet, nineteen drops of sterile water are added. In the laboratory the cells are sedimented and one drop of the clear fluid is mixed with one drop of a bouillon culture or aqueous suspension of typhoid bacilli, giving as nearly as can be obtained a dilution of 1 : 40. If not unnecessarily agitated, the corpuscular elements will lie mostly at the bottom, and the supernatant fluid may be, in a short time, clear. When the mixture has not cleared, sedimentation may be hastened by the use of the centrifuge. Accurate dilution may be assured by the use of the white cell pipet of the Thoma-Zeiss counting apparatus. The dilution made with distilled water is 1 to 20; this mixture is blown out

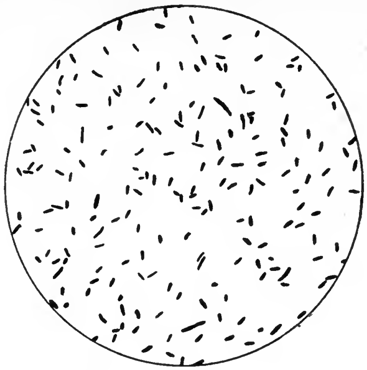


FIG. 452.—BACILLUS TYPHOSUS; WIDAL'S TEST; NEGATIVE REACTION.

Hanging-drop culture, prepared as directed on page 918. The bacilli are actively motile throughout the field.

FIG. 453.—BACILLUS TYPHOSUS; WIDAL'S TEST; POSITIVE REACTION.

Large clumps of motionless bacilli separated by open spaces. The few bacteria outside the clumps are devoid of motility.

into a small pipet or tube, which is sent to the laboratory and examined as directed above.

The time limit is as important as the dilution; usually, by the microscopic method, if the reaction, in dilutions of 1 to 40 or 1 to 50, is not well advanced or complete in thirty minutes, the test may be considered negative.

Appearance of the Reaction.—If the reaction is positive large clumps of motionless, agglutinated bacilli, which appear as irregularly shaped islands, separated by open spaces containing, perhaps, a few isolated bacteria, whose power of propulsion is either decidedly inhibited or entirely lost.

If the reaction be negative, the bacilli appear as actively motile rods, darting across the field in every direction and showing no tendency to form into masses, although occasionally small clumps of the microorganisms may be noted. In negative reactions, however, clump formation never progresses to any marked degree, and motility persists, regardless of the time during which the specimen is watched. If any

doubt exists as to the nature of a reaction, a "control" slide should be prepared with normal blood and typhoid bouillon, for purposes of comparison. (See Figs. 452, 453, 454.)

The time required for the completion of a reaction varies, but in a general way it may be said that typhoid blood will cause definite clumping and loss of motility of the typhoid bacilli within thirty minutes in the great majority of instances. In some cases a longer time will be necessary before a correct interpretation of the test can be made. *A reaction may not be classed as positive unless both clump formation and loss of motility coexist, and those reactions in which either of the phenomena are wanting may not be called typical.*

For the *macroscopic method* small test-tubes, the lumina of which should not exceed 0.5 to 0.7 cm., are used. The examination should be made in series, and for this purpose the tubes may be arranged side by side. The first tube should contain the bacterial emulsion alone. The second tube forty parts of the bacterial emulsion and one part of

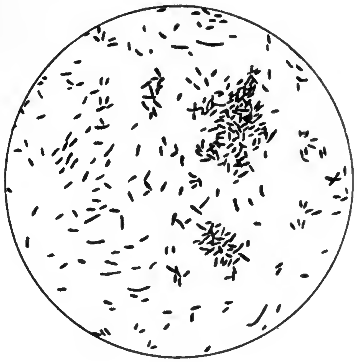


FIG. 454.—BACILLUS TYPHOSUS; WIDAL'S TEST; A PSEUDO-REACTION.
A few small clumps of bacilli having impaired motility. Persistent motility of the bacteria in other parts of the field occurs.

the suspected serum. The third tube receives one part of normal serum and forty parts of the bacterial emulsion. Other tubes may be used containing higher dilutions of the suspected serum. In the presence of a positive reaction, the bacteria collect in minute flocculi (agglutination) and finally fall to the bottom of the tube (precipitation). The reaction should be complete in from twelve to twenty-four hours.

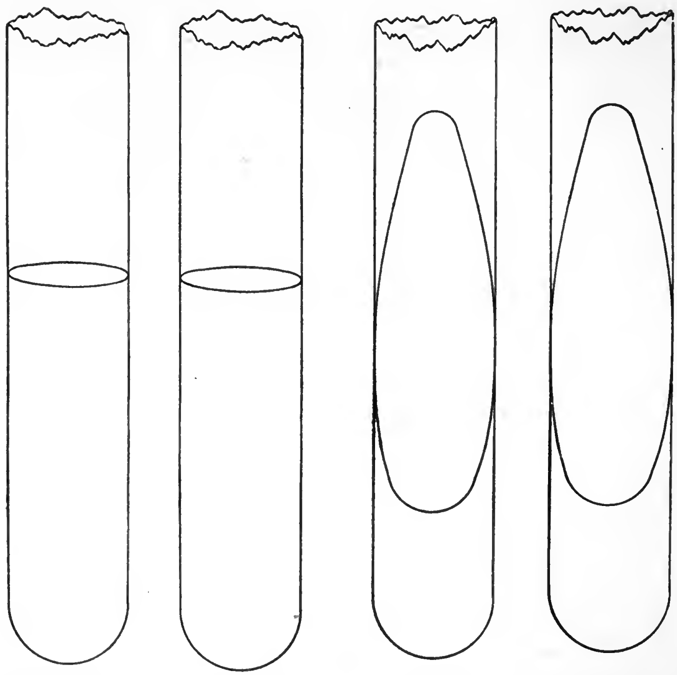
Systematic Records.—In order to render comparable studies made by different investigators, as well as for comparison of the characteristics of different bacteria, it becomes necessary to select some definite order of study and a method by which accurate records may be kept. The method which follows presents nothing original, and is that in use in the laboratories under the author's supervision. The entire blank, as well as the outline drawings of culture tubes (*b*, *c*, *d*, *e*, table on p. 932), are supplied to the student, and on these blanks he draws in black, or better in color, the cultural peculiarities of the microorganism under investigation. For noting the changes observed in the culture from day to day the drawings made each day are kept, and the

entire series clamped or gummed together for filing. The table not only affords a satisfactory means for recording the characteristics of an organism, but also indicates what data should be worked out, and the usual sequence in which the results attained are recorded.

TABLE ILLUSTRATING METHOD OF RECORDING THE PRINCIPAL CHARACTERISTICS OF AN ORGANISM.

(A) Where found.
(B) Morphology. (*a*) Form, (*b*) size, (*c*) arrangement.
(C) Stains. Reaction to Gram's method of staining.
(D) Motility { (1) Flagellate. (2) Nonflagellate.
(E) Method of reproduction.
(F) Products of growth: (*a*) Acids, (*b*) alkalies, (c) odor, (*d*) color, (*e*) gases, (*f*) enzyme, (*g*) indol, (*h*) toxin, (*i*) other chemicobiologic reaction or product.
(G) Characters of growth on: (*a*) Plates

MAKE DRAWING.



(*b*) BOUILLON. (*c*) GELATIN. (*d*) AGAR. (*e*) BLOOD-SERUM. (*f*) SPECIAL MEDIUM.

(H) (*a*) Aerobic, (*b*) anaerobic $\begin{cases} \text{(1) Facultative.} \\ \text{(2) Obligate.} \end{cases}$

(I) Reaction of medium best adapted to its growth. Reaction of cultures in milk.

(J) (*a*) Optimum temperature (*b*) thermal death-point $\begin{cases} \text{(1) Moist heat.} \\ \text{(2) Dry heat.} \end{cases}$

(K) Influence of antiseptics and disinfectants.

(L) Pathogenesis

(M) Immunity, method of securing, duration, blood characteristics in and influence of blood-serum of immune animal on the organism.

(N) Remarks: Peculiarities not embraced in foregoing form.

CHAPTER II.

MICROSCOPIC EXAMINATION OF URINE.

Collection of Sample.—The amount of urine necessary for the examination depends somewhat upon the object of the examination and the condition of the urine. In most instances at least 200 c.c. should be submitted to the examiner. For chemic examination a mixed twenty-four hours' sample is usually recommended, but for microscopic study a succession of samples collected at different hours during the day, and especially morning and evening, offers certain advantages. Bryson has shown that for the demonstration of tubercle bacilli residual urine offers better results than the tidal. It is well known that purulent urines, and especially those rich in bacteria, particularly the colon bacillus, exert a lytic action on structural elements coming from the kidney, and especially on casts; such specimens should be examined shortly after voiding. The urine should be collected in a perfectly clean bottle and delivered at once. When tubercle bacilli are to be looked for, or when any bacteriologic examination is contemplated, the container should be disinfected, all parts of the external genital organs that are likely to come in contact with the urine should be cleansed and the urine drawn with a thoroughly cleansed and sterile catheter. Smegma bacilli are so abundant in the external genital organs of the female that it is best to use extra precautions, and, if possible, to remove the urine by means of a glass catheter that has been sterilized in a hot-air oven at a sufficiently high temperature to carbonize any bacteria that may be upon or within it. As soon as received, the urine should be sedimented. This may be accomplished by permitting it to stand in a conic glass, such as is shown in figure 456. A better and more convenient means for securing sedimentation is by the centrifuge. Of the various forms of centrifuge, those in which the power is supplied by the hand or turbine are to be preferred.

Method of Conducting the Examination.—As soon as the sediment has been secured by either of the methods previously indicated, a sterile pipet, closed by the finger at the upper end, is cautiously introduced through the supernatant fluid into the sediment; the finger is slowly drawn to one side, permitting a few drops of sediment to enter. The finger is then held tightly over the pipet, which is at once withdrawn from the urine. The fluid on the outside of the pipet is then removed with a cloth or paper, and, holding the pipet perpendicularly, a small drop is placed on the slide and a cover-glass applied. Drain off excess of fluid with blotting-paper, and examine with $\frac{2}{3}$-inch and $\frac{1}{4}$- or $\frac{1}{6}$-inch objectives. While a number of methods have been devised by which the organized constituents of urine may be stained, the student had best familiarize himself with unstained preparations, although for special purposes staining may be necessary. An important precau-

tion is never to flood the field with light. The illumination should be even but subdued; an excess of light renders hyaline casts, red blood-cells which have lost their hemoglobin, and other shadowy structures invisible. The light is best reduced by lessening the opening in the iris diaphragm.

Preservation of the urine may be aided by adding a crystal of thymol, camphor, or menthol. If it be desired to preserve the sediment, this is best accomplished by carefully decanting the supernatant fluid and adding an equal quantity of a saturated aqueous solution of potassium acetate, allowing this to remain forty-eight hours, again decanting, and adding fresh acetate solution. After repeating this three times, no difficulty will be found in preserving casts, blood, epithelium, etc., present in the sediment. Casts may be preserved indefinitely in chloral, provided they have been washed according to the methods just indicated. The chloral solution should have a strength of about twenty grains to the ounce of water, and should exceed in volume one hundred times the volume of the sediment to be preserved. Fischel preserves casts in a mixture of equal parts of glycerin and distilled water, saturated with thymol.[1]

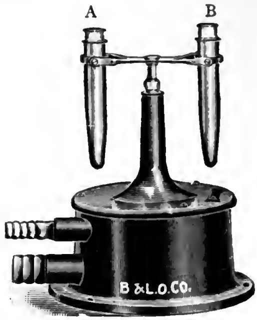


FIG. 455.—WATER CENTRIFUGE. The number of revolutions depends on the water pressure and on the size of the supply pipe. A pipe at least ½ of an inch should be used. The ordinary city pressure is about 25 pounds; with ½-inch pipe this will give 1200 revolutions a minute; 30 pounds will give 1400; 35 pounds, 1500. A thousand revolutions a minute are sufficient for urine sedimentation. Tubes A and B hold 30 c.c. each.

ORGANIZED SEDIMENT (*Cellular Constituents*).—*Red Blood-corpuscles.*—When these corpuscles occur in large numbers and in good condition without being intimately blended with the urine, they are usually from the bladder or urethra; but when they do not form a red sediment after many hours' standing, and have lost their coloring-matter and appear as pale yellow, washed-out rings (phantom corpuscles of Traube), especially if associated with blood-casts, the hemorrhage has probably occurred in the substance of the kidney, renal pelvis, or ureters.

Leukocytes in urine are usually indicative of some inflammatory condition of the conducting passages. They rapidily disappear in alkaline urines; when freshly voided, they may show ameboid movement. While other forms are not infrequently found, the polynuclear usually predominates. Fragmented and granular cells are commonly present.

Epithelium.—(Make drawings of different forms.)

Squamous epithelium.

Transition epithelium.

Epithelium from bladder.

Urinary Casts (see p. 639).

I. Those consisting of cells.

II. Those that consist of the products of cellular change.

III. Hyaline casts.

[1] For the permanent preservation of tube casts for microscopic mounts, see Boston, "N. Y. Med. Jour.," November 4, 1899. For chemistry of tube-casts and other details, see Coplin, "Publications from the Laboratories of the Jefferson Medical College Hospital," 1904, vol. i. For structure, origin, and significance of casts, see p. 639.

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Examine with $\frac{1}{4}$-inch or $\frac{1}{6}$-inch objective and make drawings of—

Blood-casts,
Epithelial casts,
Granular casts,
Waxy casts,
Fatty casts,
Hyaline casts,
Pus-casts,
Bacterial casts,
Cylindroids,
False casts, composed of urates or crystals,
Casts from seminal tubes.

Spermatozoa are thread-like bodies, 50 μ long, provided with a head and a long, tapering, tail-like extremity.

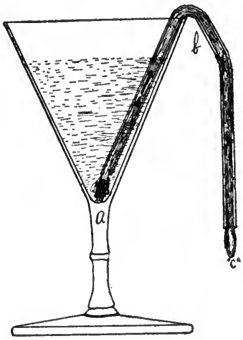

FIG. 456.—CONIC GLASS SUITABLE FOR THE SEDIMENTATION OF URINE.—(*Coplin and Bevan.*)

In position is shown a candle-wick filter for securing urinary sediment. The filter consists of a glass tube so bent that the longer arm is outside and opens below the level of the bottom of the conic glass. Through the bent glass tube are drawn a few strands of candle-wick to fill the tube rather tightly. By capillarity the urine rises in the bent tube and eventually flows over; in so doing it deposits all the sediment on that end of the candle-wick which is at the bottom of the glass. This is gently brushed over a number of slides, cover-glasses are applied and the slides examined at once.

FIG. 457.—CENTRIFUGE WITH HEMATOCRIT ATTACHMENT.

The attachment for sedimenting liquids such as urine is shown in position for use. This may be lifted off and the hematocrit attachment shown in the upper part of the figure substituted in the place of sedimenting attachment shown in position. There are two gears, one for sedimenting blood known as the high gear, and which gives 10,000 to 14,000 revolutions a minute; the lower gear, for sedimenting urine, giving from 2500 to 4000 revolutions a minute. The crank is easily transferred from one gear to the other.

Their constant deposit indicates spermatorrhea. They are easily identified in urinary sediment, or may be stained as follows: Spread a thin layer of the sediment on a clean cover-glass; dry without heat; stain in carbolfuchsin for two seconds; wash in water; *dry*, and mount in balsam.

Occasionally fragments of papilloma may be recognized in the urine. If the specimen has been drawn with a catheter, the eye of the instrument may contain shreds of such growths.

Nonpathogenic Fungi:

Molds, or large segmented rods.

Yeast plants (Saccharomyces urinæ and other yeasts) are arranged in bead-like forms with budding cells attached.

Bacteria of decomposition.

Pathogenic Fungi.—*Tubercle Bacilli* (see p. 144).—In all cases of purulent urine accompanied by anemia, wasting, and evening rise of temperature, the urinary sediment should be examined for tubercle bacilli.

Purulent deposits of tuberculous urine should be treated the same as sputum in searching for tubercle bacilli. The centrifuge aids materially in this examination. (For method of demonstration see Tubercle Bacilli.)

Gonococcus (Neisser, see p. 107).—Minute, roll-shaped diplococcus found in urine containing gonorrheal pus. (For method of staining and description see Gonococcus.)

Distoma Hæmatobium (see p. 193).—The oval eggs of this parasite, about 125 μ by 40 μ, spiculated at one end, are found accompanied by blood-cells and pus.

Filaria Sanguinis Hominis (see p. 207).—The embryos are occasionally found in chyluria. (See Animal Parasites.)

UNORGANIZED SEDIMENT (*Crystalline and Amorphous*).

Sediment of Acid Urine.—(Examine and draw the various crystals.)

Uric acid (whetstone crystals).
Oxalate of lime (envelop crystals).
Hippuric acid.
Urate of soda.
Tyrosin and leucin.
Soaps of lime and magnesium.
Amorphous deposits.
Urates.
Brown and yellow concretions.

Sediment from Alkaline Urine.

Triple phosphates (coffin-lid crystals).
Urates of Ammonium (hedge-hog crystals).
Indigo.
Cholesterin.
Amorphous deposits.
Phosphate of lime.
Carbonate of lime.

ILLUSTRATIONS OF VARIOUS URINARY SEDIMENTS.[1]

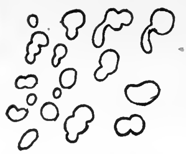

FIG. 458.—PHANTOM AND DISTORTED RED BLOOD-CELLS FOUND IN URINE, MOST COMMONLY THAT OF RENAL HEMATURIA.—(*Landois.*)

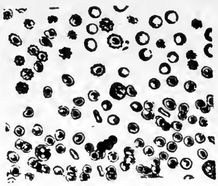

FIG. 459.—BLOOD-CELLS IN THE URINE.—(*Gould.*)

The cells that appear almost normal could not have been subjected to the action of the urine but for a short time.

FIG. 460.—BLOOD-CELLS IN THE URINE, LYMPH-CORPUSCLES, LEUKOCYTES OR PUS-CELLS, AND CRYSTALS OF TRIPLE PHOSPHATE. × 350 diameters.—(*Landois.*)

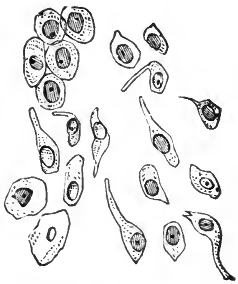

FIG. 461.—EPITHELIUM FROM THE CONDUCTING PART OF THE URINARY APPARATUS, MOSTLY FROM THE BLADDER.

Note in the upper right quadrant of the figure the cells that resemble renal epithelium.

FIG. 462.—EPITHELIUM OF THE RENAL TYPE.

The four cells below and to the left are fatty. This form of epithelium will be found on casts and free in the urine. It will be noted, however, that it so closely resembles epithelium from one layer of the conducting apparatus that the diagnosis of free renal epithelium must always be open to criticism. See figure 461 epithelium from the bladder.

[1] Experience has convinced the writer that the best way to learn to recognize the various urinary sediments is to take as good an illustration, or series of illustrations, as can be secured, and work at the microscope with the illustrations at hand until able to recognize all the ordinary forms.

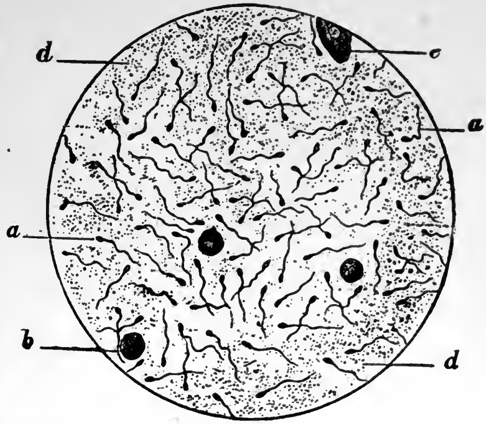

FIG. 463.—SEMINAL ELEMENTS, SOME OF WHICH MAY BE FOUND IN URINE.
a, *a*. Spermatozoa. *b*. Seminal cells. *c*. Epithelium. *d*, *d*. Seminal granules.

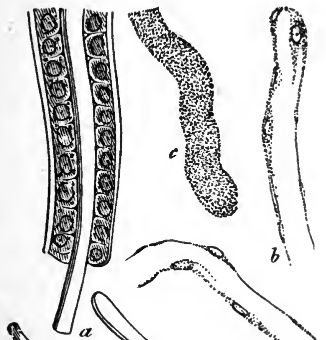

FIG. 464.—ILLUSTRATING THE FORMATION OF CASTS. (*Rindfleisch*.)

a. Hyaline cast in place. If it comes away bringing nothing with it, it will remain a hyaline cast. If it brings epithelium, it will be an epithelial cast; if the epithelium is granular, it will be a granular cast; if fatty, a fatty cast. *c*. Granular cast. The two casts in the lower corner, and to the left, are hyaline; the remaining casts are largely hyaline but bear a few epithelial cells.

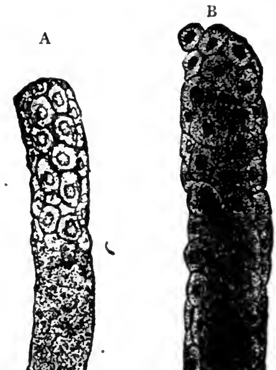

FIG. 465.—EPITHELIAL CASTS.—(*Landois*.)

A. Epithelial cast, the lower end of which is coarsely granular. B. Epithelial cast in which the epithelial cells, though themselves granular, have not broken up.

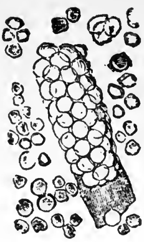

FIG. 466.—BLOOD-CELLS AND BLOOD-CAST.—(*Landois.*)

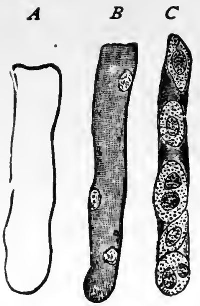

FIG. 467.
A. Hyaline cast. *B*. Hyaline cast with a few attached leukocytes. *C*. Hyaline cast with attached epithelium, truly an epithelial cast.—(*Landois.*)

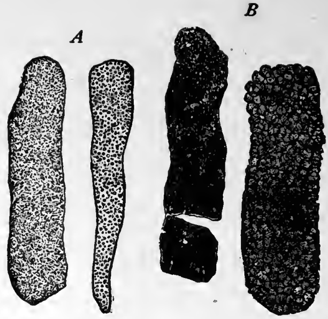

FIG. 468.—GRANULAR CASTS.—(*Landois.*)
A. Granular casts in which the granules are fine and the dissolution of the epithelial cells is complete. *B*. Granular casts in which the granules are coarse and the outlines of the epithelial cells at points faintly distinguishable.

FIG. 469.
A. Cast made up almost purely of leukocytes. *B*. Casts composed of acid sodic urate; crystalline casts.— andois.)

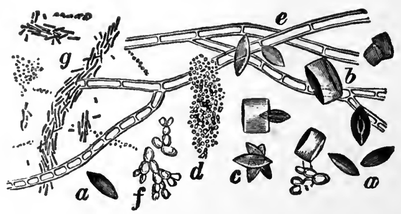

FIG. 470.
a, *a*, *b*, *c*. Crystals of uric acid. *d*, *g*. Zooglea masses of cocci and bacilli. *e*. Mold. *f*. Yeast.—(*Landois.*)

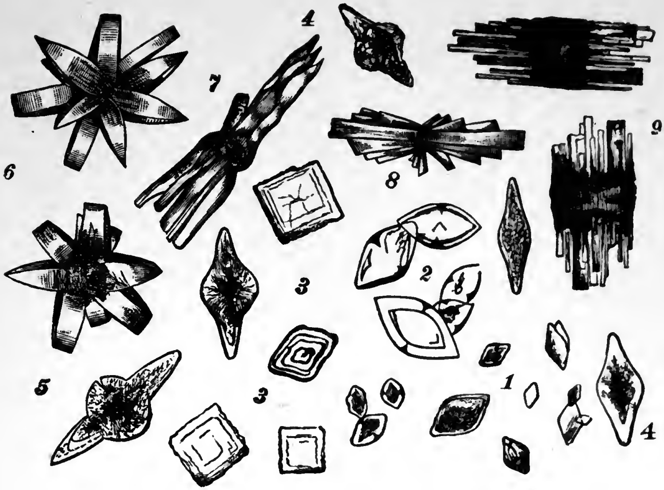

FIG. 471.—SOME FORMS OF URIC ACID.

1. Rhombic crystals. 2. Whetstone forms. 3. 3. Quadrate forms. 4, 4, 5. Irregular forms. 6, 8. Groupings into roset forms. 7, 9. Bundle forms, precipitated by adding hydrochloric acid to the urine. The crystals may be pigmented or lightly colored brownish-yellow; the pigment is presumed to be uroerythrin. also called urochrome.—(*Landois.*)

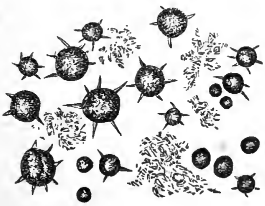

FIG. 472.—ACID AMMONIUM URATE.

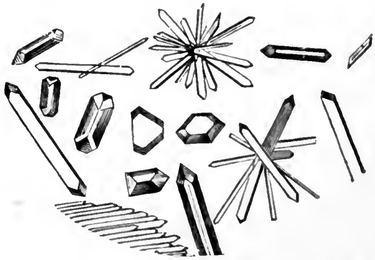

FIG. 473.—HIPPURIC ACID. FOUR-SIDED PRISMS WITH TWO OR FOUR BEVELED EDGES.—(*Gould.*)

FIG. 474.—SOME DEPOSITS IN ACID FERMENTATION OF THE URINE.—(*Landois.*)
a. Bacteria. *b*. Amorphous sodic urate. *c*. Uric acid. *d*. Calcium oxalate.

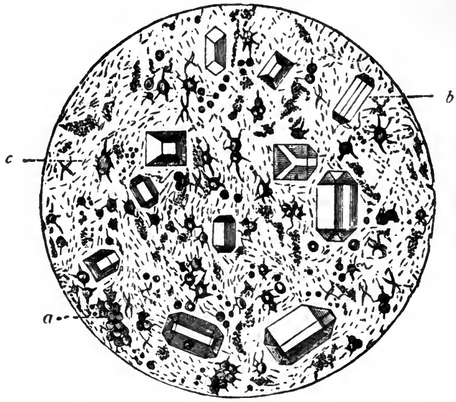

FIG. 475.—SOME DEPOSITS FROM AMMONIACAL URINE (ALKALINE FERMENTATION).
a. Acid ammonium urate. *b*. Ammoniomagnesium phosphate. *c*. Bacteria.

FIG. 476.—WHETSTONE AND IRREGULAR CRYSTALS OF URIC ACID.—(*Gould.*)

FIG. 477.—AMMONIUM URATE. "HEDGE-HOG" CRYSTALS.—(*Gould.*)

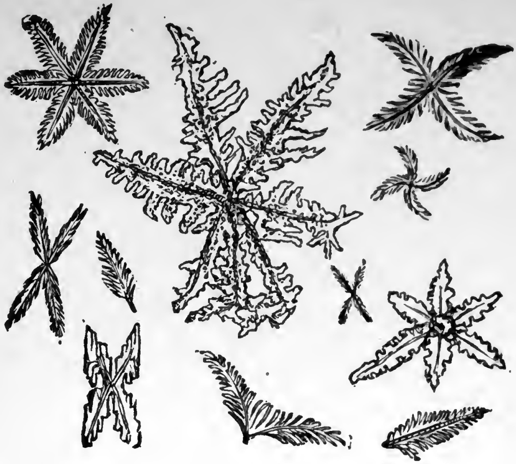

FIG. 478.—STELLATE AND FEATHERY CRYSTALS OF TRIPLE PHOSPHATE.—(*Tyson.*)

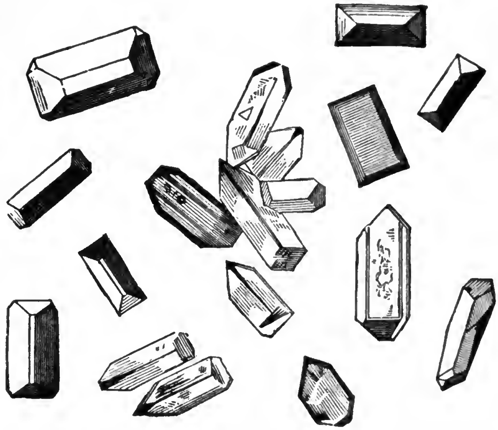

FIG. 479.—FORMS OF CRYSTALS OF THE AMMONIOMAGNESIUM PHOSPHATE.—(*Tyson.*)

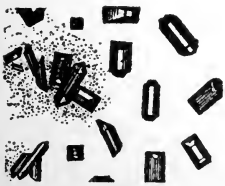

FIG. 480.—AMMONIOMAGNESIUM PHOSPHATE (TRIPLE PHOSPHATE).—(*Gould.*)

Triangular prisms with beveled edges; "coffin-lid" crystals.

FIG. 481.—MAGNESIUM PHOSPHATE.—(*Gould.*)

Elongated rhombic tablets, which may be fused together in variously formed masses.

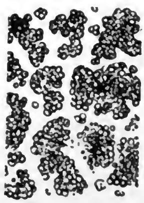

FIG. 482.—AMORPHOUS GRANULES OF CALCIUM CARBONATE.—(*Gould.*)

FIG. 483.—OXALATE OF LIME

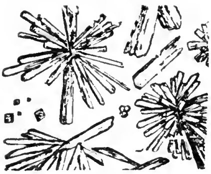

FIG. 484.—AMORPHOUS GRANULES, WEDGE-SHAPED CRYSTALS, SOME ARRANGED IN ROSETS OF CALCIUM PHOSPHATE.—(*Gould.*)

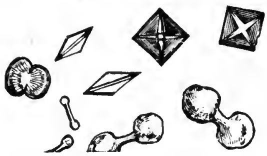

FIG. 485.—DUMB-BELL AND OCTAHEDRAL CRYSTALS OF CALCIUM OXALATE.—(*Gould.*)

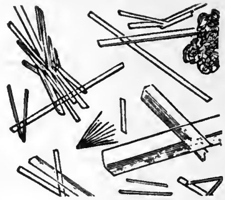

FIG. 486.—CALCIUM SULPHATE ELONGATED TRANSPARENT NEEDLES OR TABLETS.—(*Gould.*)

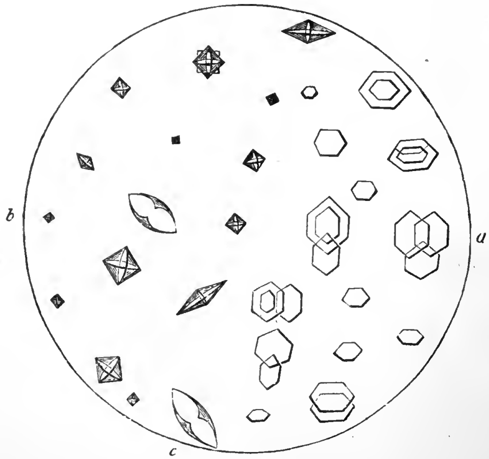

FIG. 487.

a. Crystals of cystin. *b*. Crystals of oxalate of lime. *c*. Hour-glass forms of *b*

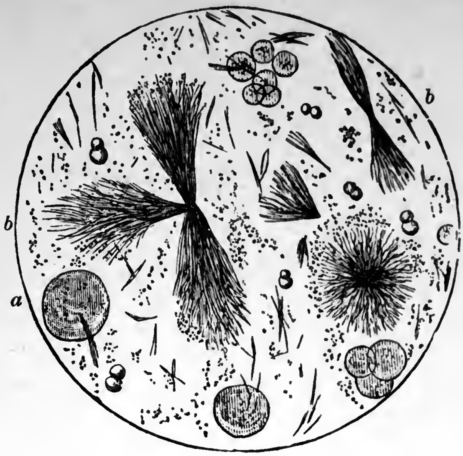

FIG. 488.
a. Leucin balls. *b*, *b*. Tyrosin sheaves.

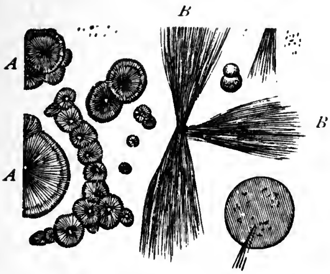

FIG. 489.—LEUCIN AND TYROSIN.
A, *A*. Leucin; yellowish, highly refracting spheres, with radiating lines. *B*, *B*. Tyrosin, needles and sheaf.

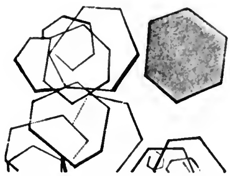

FIG. 490.—CYSTIN, SIX-SIDED PLATES, OFTEN SUPERIMPOSED.—(*Gould*.)

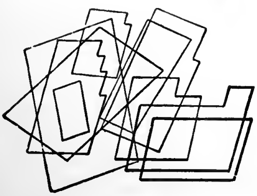

FIG. 491.—CHOLESTERIN.—(*Landois*.)

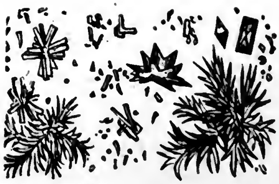

FIG. 492.—INDIGO.—(*Gould*.)
Amorphous granules, fine needles, and crystals of a blue color.

CHAPTER III.

TECHNIC OF SPUTUM EXAMINATION.

Collecting the Specimen.—Great care should be exercised in obtaining the sputum for examination. Sputum collected immediately after eating usually contains particles of the food, which unnecessarily complicate the examination. The first sputum raised in the morning is to be preferred. The patient should be instructed to avoid collecting mucus brought from the nose and pharynx. Findlay obtains sputum from young children by wrapping the finger with a piece of gauze, irritating the epiglottis by the gauze-wrapped finger, and sweeping out of the mouth any sputum that results from the induced coughing. The amount of sputum to be obtained will vary with circumstances: while a very small amount may be examined and give satisfactory results, five or ten cubic centimeters or more should be obtained when possible. The patient should expectorate directly into a small stone cup or sterilized salt-mouth bottle; as soon as a sufficient quantity of sputum has been collected, the container should be at once sealed with

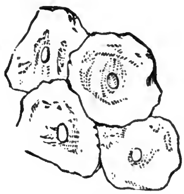

Fig. 493.—Squamous Epithelium.
Often found in sputum and in urine. In the former it is from the mouth or pharynx. In urine it is usually from the vagina.

adhesive plaster or tightly corked, and labeled. When ready for examination, the sputum should be poured upon a piece of ordinary window glass with the under side painted black, or into a Petri dish placed over a blackened surface. Upon this black surface the small, white, opaque portions, which are best for examination, can be readily seen, removed by forceps or platinum hook, and placed in the center of a glass slide. A cover-glass is laid on the specimen, and slight pressure made to obtain a uniform layer.

White blood-corpuscles are always present in sputum; eosinophiles occur in certain forms of asthma and chronic bronchitis, and, according to Teichmüller, in two-thirds of the cases of pulmonary tuberculosis; in the latter condition he believes they have some prognostic value, being most abundant in patients that are doing well.

Red Blood-corpuscles.—Their presence in small numbers is not significant. In pneumonia they occur as pale, discoid bodies, and

in hemoptysis the sputum may consist almost entirely of red corpuscles.

Epithelium.—Squamous, from the mouth.

Ciliated, usually from the trachea and bronchi.

Alveolar, from the alveoli of the lungs.

Elastic Fibers.—When these fibers display an alveolar arrangement, they have been derived from the pulmonary alveoli, and indicate a destruction of lung tissue.

They occur in tuberculosis and bronchiectasis, and occasionally in

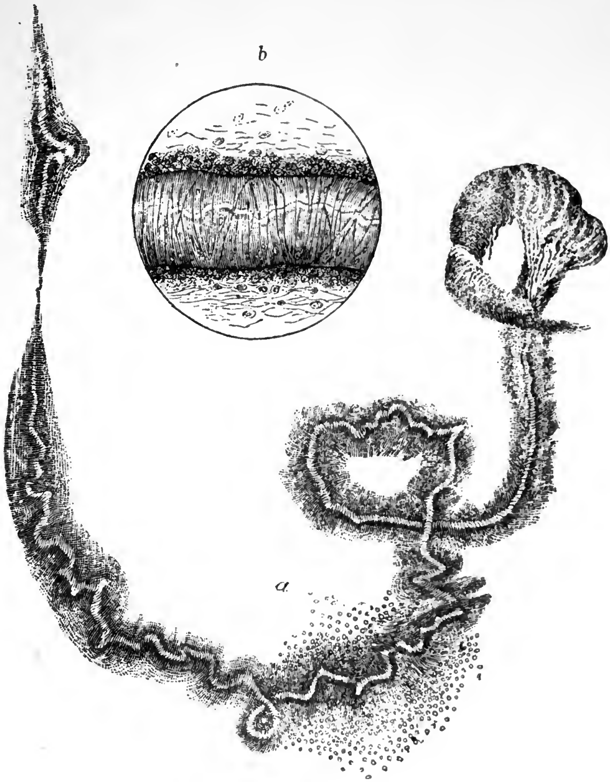

FIG. 494.—CURSCHMANN'S SPIRALS.—(*Schmaus.*)
a. × 80 diameters. *b.* × 300 diameters.

pulmonary abscess, gangrene of the lung (some cases), pneumonia and destructive processes attacking the air-passages and lungs. The slide of sputum is prepared in the usual way, and examined with a $\frac{1}{6}$-inch objective. The elastic fibers exhibit a double contour, are dark colored, slightly curved, and vary much in length and breadth. They can be most readily collected for demonstration by rapid sedimentation in a centrifuge.

The sputum contains extraneous pigments in the pneumonoconioses and altered blood-pigments in chronic pulmonary congestion.

Curschmann's spirals are found in sputum of asthmatic patients, and appear as thick white bodies having a twisted tubular form. When examined with a low power, they show a central, highly refracting, twisting thread, around which is a meshwork of delicate fibers. They require no stain.

Fibrinous casts are tree-like casts of the terminal bronchial tubes, found in bronchitis and pneumonia, and composed of fibrin or mucin containing entangled cellular elements. (See Fibrinous Inflammations of Mucous Membranes.)

Charcot-Leyden Crystals.—These crystals are colorless, have a pointed octahedral form, and are found chiefly in the semi-solid, grayish-yellow pellets discharged during an asthmatic attack.

The diagnosis of pulmonary cancer from *neoplastic fragments* found in the sputum has been made by Cornil.

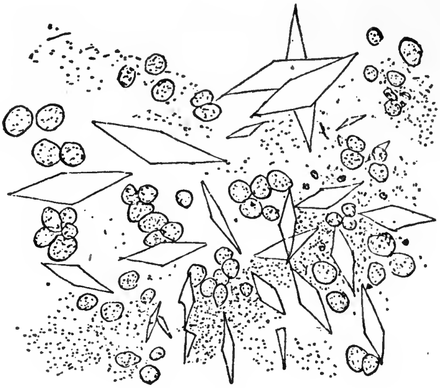

FIG. 495.—CHARCOT-LEYDEN CRYSTALS.—(*Landois.*)

Tubercle Bacillus.—(For technic of examination see article on Bacteriology.)

Bacillus of leprosy occasionally occurs in sputum. (For technic of examination see article on Bacteriology.)

Pneumobacillus (Friedländer), *Pneumococcus* (Fränkel), *Actinomyces, Bacillus anthracis, staphylococci, streptococci, Bacillus influenzæ, Bacillus mallei, Bacillus pestis, Bacillus typhosus,* etc.[1]—(For technic of demonstration see article on Bacteriology.)

Fragments of *echinococcus cysts*, the *scolices* or *hooklets* of the parasite, the eggs of the *Distoma pulmonale*, rarely the parasite, are occasionally found in sputum. The Amœba histolytica and possibly other amebæ are occasionally encountered; Schmidt has observed non-pathogenic flagellates (trichomonads) in the sputum.

[1] For an exhaustive review of the bacterial flora of the sputum see Kerschensteiner ("Deut. Arch. f. klin. Med.," 1902, vol. lxxv); Lenhartz ("Postgraduate," 1902).

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